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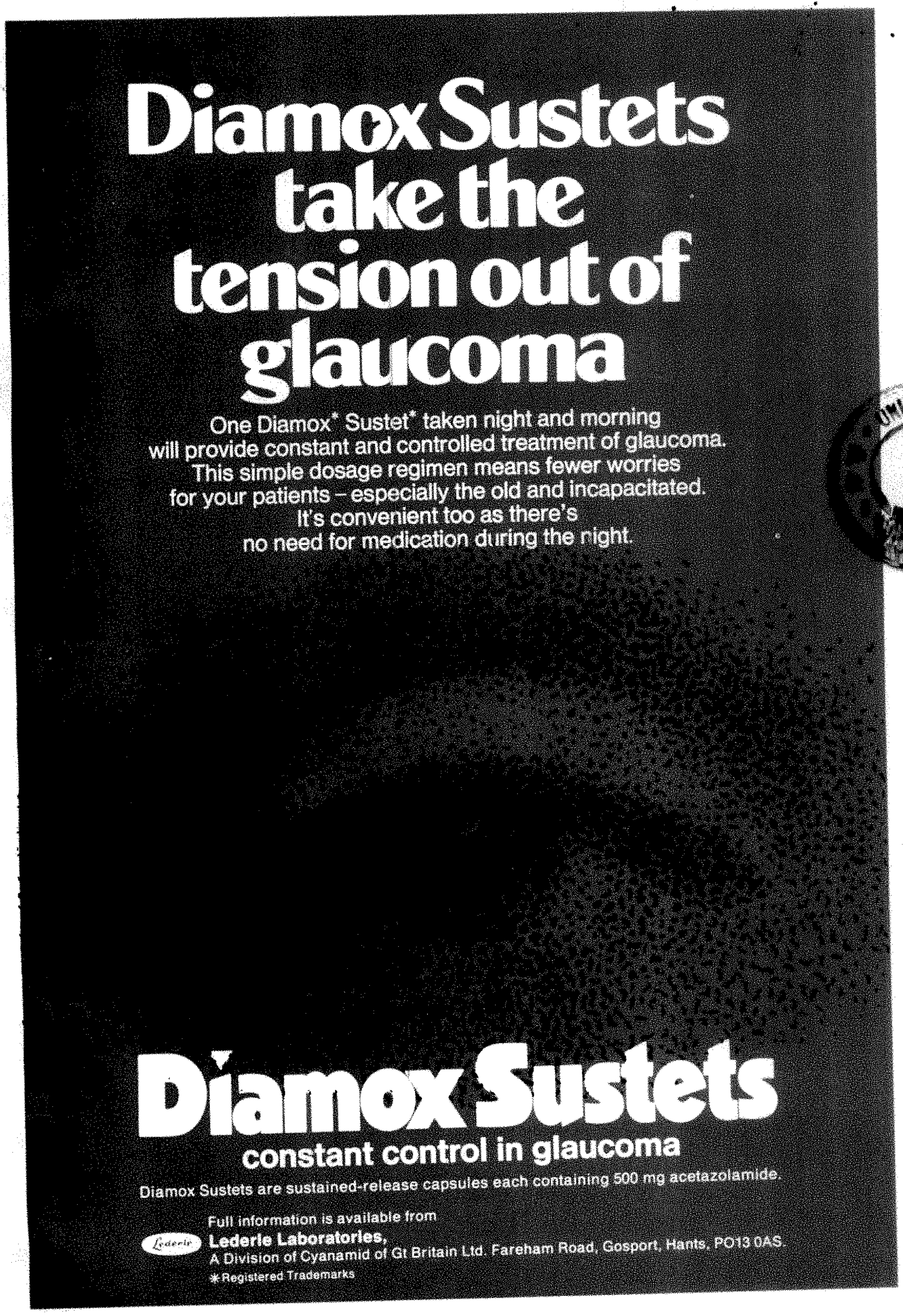

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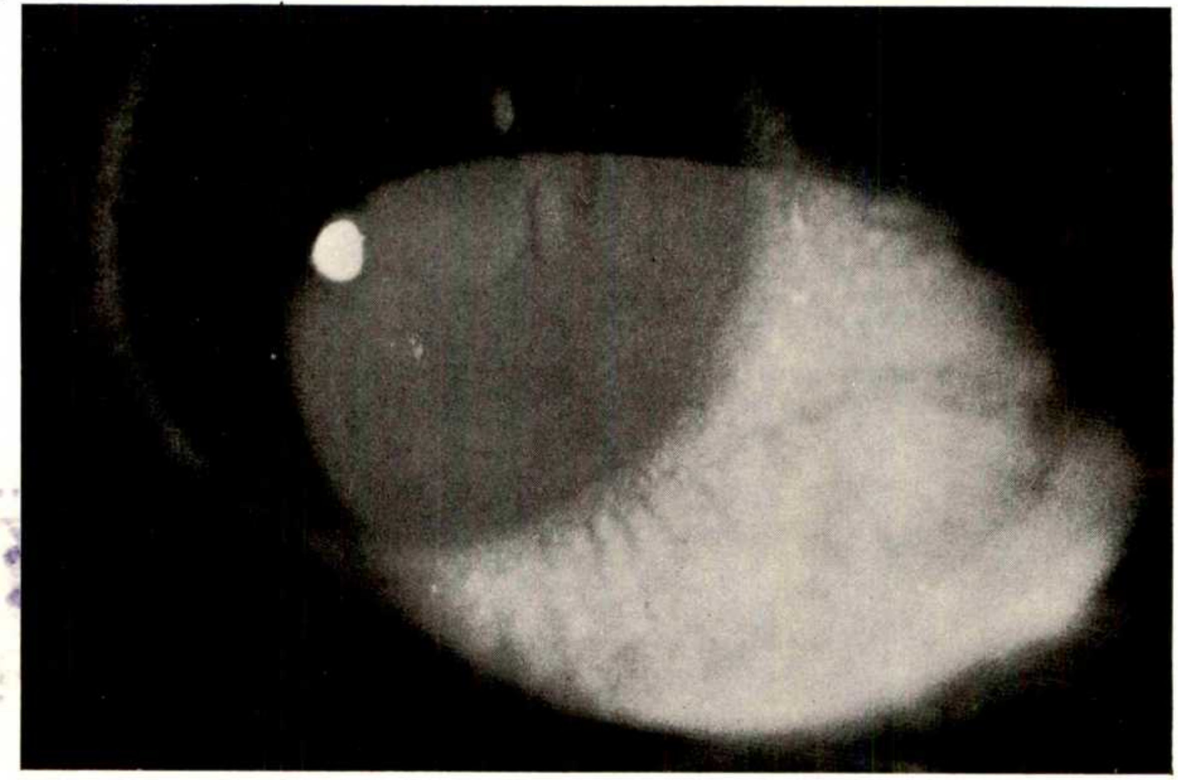

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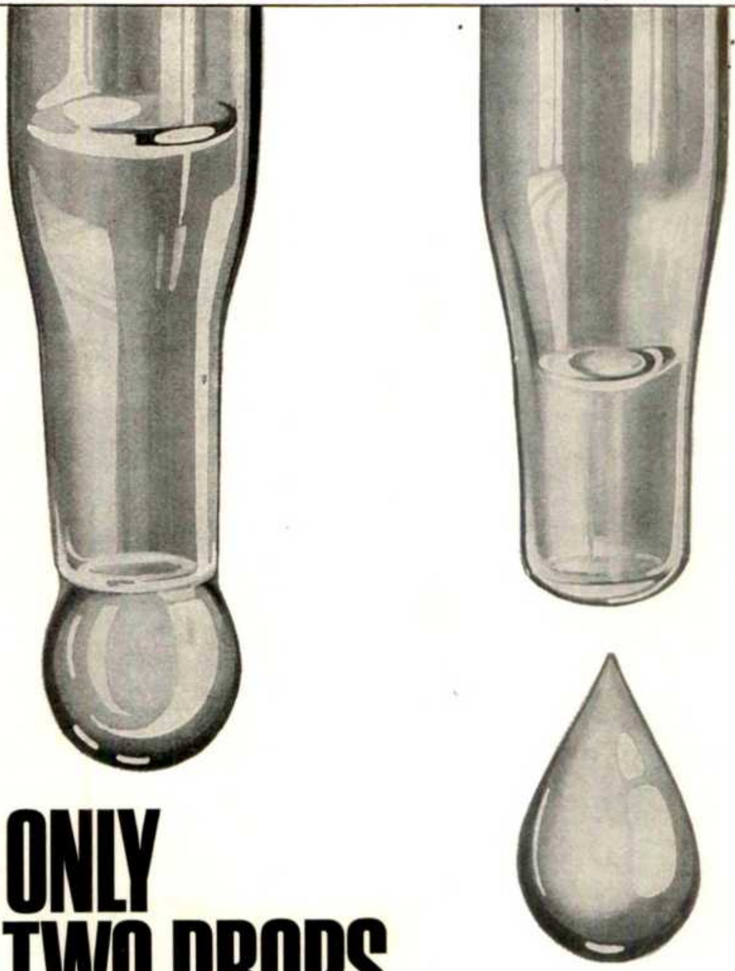

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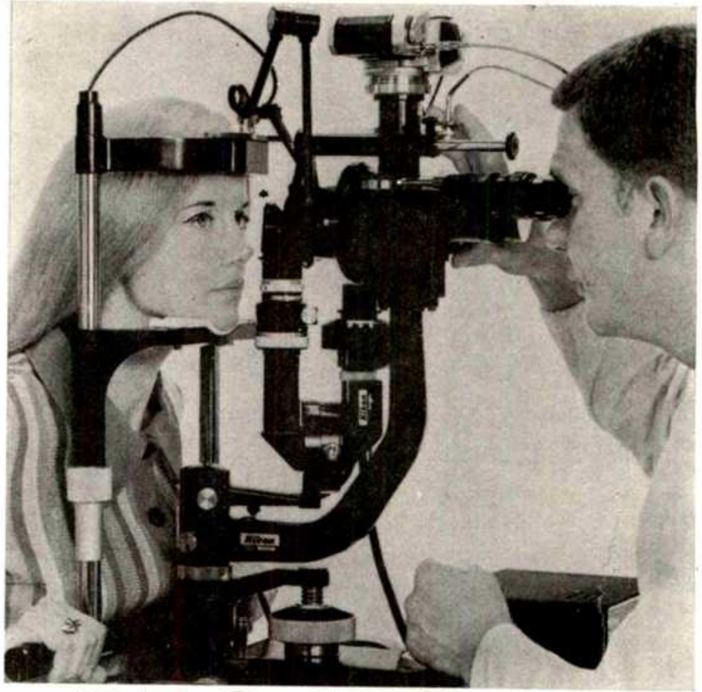

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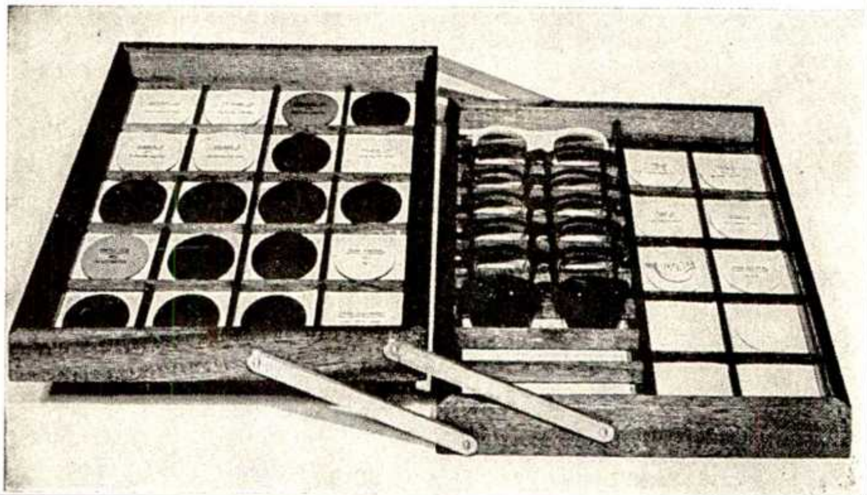

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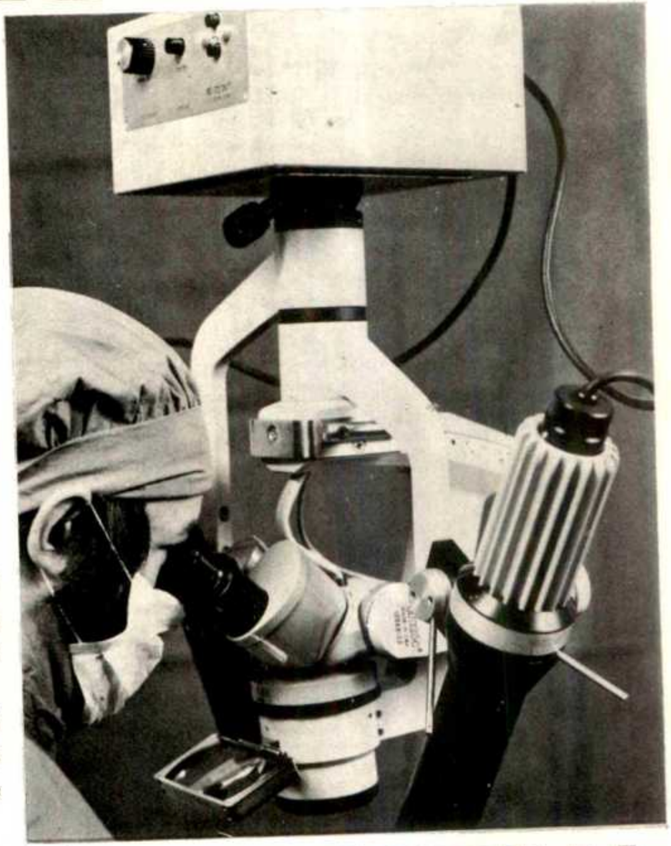

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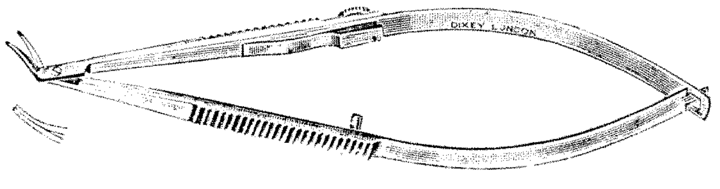

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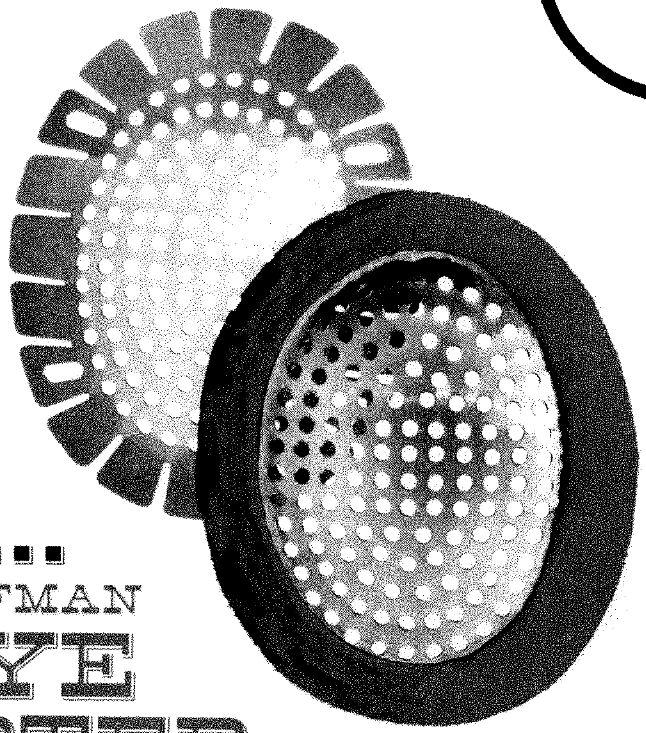

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Editorial: Onchocerciasis

More than 3000 publications on the subject of onchocerciasis testify to its importance and complexity. O'Neill (1875) fired the opening shot, when he linked the presence of skin microfilariae with the chronic skin disease 'craw-craw' on the Gold Coast. Leuckart (1891) connected the microfilariae with the adult worms in skin tumours (onchocercomata) excised from West Africans, although at that time no connexion was made between the skin disease and eye troubles. Across the Atlantic in Mexico and Guatemala, however, attention in the early 1900s began to be focused on a chronic skin disease associated with blindness called 'erisipela de la costa'. Robles (1917, 1919), a Guatemalan physician, related this to *O. volvulus,* while his ophthalmic colleague Pacheco-Luna (1918, 1919) connected the onchocercomata and the microfilariae to the blinding kerato-iridocyclitis, so characteristic of the Central American form of the disease that Brumpt (1919) called it *O. caecutiens.* Some 15-18 years later Hissette (1932) in the Belgian Congo and Bryant (1935) in the Sudan recognized that the African and Central American diseases were the same—but are they? Is onchocerciasis a disease of multicentric origin, or was it imported from Africa together with the slaves and the soldiers, beginning with Cortes in 1519 and ending with Maximilian in 1867? (Torroella, 1964).

The next major difficulty is to assess the importance of onchocerciasis as a public health problem. Undoubtedly it is very widespread, probably involving 30-50 million persons in equatorial Africa, 250 000 in Central America, and a few thousand expatriates in whom the adult worms are living out their life-span of 15 years or so, probably producing one million microfilariae annually for most of this period. Perennial and heavy infection transforms the ocular situation from a benign parasitosis to a blinding disease, principally in those who are over 40 years of age. In some villages in the Sudan-savanna regions the blindness rate may be 34 per cent (Anderson, Fuglsang, Hamilton, and Marshall, 1974). A median figure for all those millions of people infected who end up blind would be around 2 per cent or one million in Africa, 5000 in Central America, and none among the expatriates—who should be made clearly aware that a diagnosis of onchocerciasis does not sentence them to visual impairment, but only to a chronic pruritic skin complaint.

Among the scientific problems still unsolved are: why are there such marked variations in the behaviour of the disease, even between the rain forest and savanna regions of Africa, and between them and the Central American foci and also the Yemen? Are all the foci known? Both animal onchocerciasis and various species of *Simuliidae* are widely distributed over the globe, and transfer to humans may have occurred elsewhere. While the pathogenesis of the blinding kerato-iridocyclitis is fairly well understood the portals of entry of the microfilariae to the eye need further study, as do the aetiology and significance of the fundus lesions. In this issue there is an interesting study of this matter, and the authors (Bird, Anderson, and Fuglsang, 1976) are to be congratulated on taking fluorescein angiography into the African bush as part of their project.

Infestation of the anterior segment by hordes of microfilariae would be expected to interfere with intraocular fluid dynamics, but it is only from Liberia that a high incidence of chronic open-angle glaucoma in onchocercal as opposed to non-onchocercal subjects has been reported, by Neumann and Zauberman (1965), and confirmed by Langham, Frentzel-Beyme, and Zolu-Dumah Traub (1975).

What to do about onchocerciasis as a public health matter is clearly of critical importance and one hopes that the World Health Organization, in its proposal to spray insecticides from the air on the most affected areas in West Africa, for which it has a $40 million grant from the World Bank to help, is making the right decision. Further research not only into the disease process, but also into such therapeutic possibilities as slow-release diethylcarbamazine, might usefully be put in train contemporaneously.

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Morphology of posterior segment lesions of the eye in patients with onchocerciasis

A. C. BIRD†, J. ANDERSON*, AND H. FUGLSANG*
*From the Institute of Ophthalmology and Moorfields Eye Hospital†, and the Medical Research Council, Kumba, United Cameroon Republic**

Hissette (1932), Bryant (1935), and Ridley (1945) described ocular fundus changes in Central Africa which were characterized by atrophy of the pigment epithelium and choroid, and they suggested that there was an association between these lesions and infection with *Onchocerca volvulus*. More recent epidemiological and histopathological evidence supports the causal nature of this association (Rodger, 1960; Budden, 1963; Monjusiau, Lagraulet, D'Haussy, and Göckel, 1965; Anderson, Fuglsang, Hamilton, and Marshall, 1974a). Many authors, including Quevedo (1941), Clark (1947), Toulant, Robineau, and Puyelo (1950), D'Haussy, Rit, and Lagraulet (1958), and Lagraulet and Monjusiau (1964), have also recognized that optic neuritis and optic atrophy are associated with onchocerciasis. However, the pathogenesis of the posterior segment lesions remains obscure (Rodger, 1960; Budden, 1962; Quéré, Basset, Larivière, Basset, and Razafinjato, 1963; Ben-Sira and Yassur, 1972), and little attention has been given to the relative importance of optic nerve and fundus lesions as causes of blindness in onchocerciasis (D'Haussy, Boithias, and Bertet, 1954; Weyts, 1956).

The morphology of the posterior segment lesions attributable to onchocerciasis in 244 patients who were examined in the Sudan-savanna and rain-forest zones of the United Cameroon Republic is described in this paper. The study took place in March 1974 and March 1975.

Materials and methods

Altogether 331 patients were selected for examination from three sources:

(a) 85 had posterior segment lesions compatible with onchocerciasis which had been identified during a population survey carried out in 1970–72 (Anderson and others, 1974a; Anderson, Fuglsang, Hamilton, and Marshall, 1974b).
(b) 231 patients, most of whom had come spontaneously with visual complaints, were found to be heavily infected with *O. volvulus*.
(c) 15 patients were from the Bulu Blind School in the SW Province of Cameroon.

Eighty-seven patients from groups (b) and (c) were rejected from the study. In 56, the fundus was considered to be normal and no evidence of visual loss was detected, and in 31 there were fundus lesions unrelated to onchocerciasis—such as typical ocular toxoplasmosis, myopia, macular hole, and genetically-determined retinitis pigmentosa.

This report is concerned with the findings in the remaining 244 patients.

Of these, 140 came from the Sudan-savanna and 104 from the rain-forest. Of the 140 savanna patients, 58 had previously received treatment with suramin and/or diethylcarbamazine citrate (dec) under medical supervision. In the rain-forest, nine of the 104 patients had been treated similarly, and many others admitted to having taken variable quantities of dec on their own initiative.

The intensity of infection with *O. volvulus* had been assessed previously by measuring the concentration of microfilariae in weighed skin snips, and by recording the number of microfilariae seen in the cornea and anterior chamber, together with their presence in the retrolental space or vitreous (Anderson and others, 1974a).

Visual acuity was measured using the illiterate E-chart, and visual fields to confrontation were recorded in most patients. After the pupil had been dilated with mydriacil 1 per cent, the fundus was examined by indirect and direct ophthalmoscopy, and colour photographs were taken using a Kowa RC 2 fundus camera. Fluorescein angiography was performed in 210 patients. Five ml 20 per cent sodium fluorescein were injected into the antecubital vein, and photographs were taken, with a Kowa RC 2 fundus camera, at 1·5 s intervals during the initial transit of dye through the retinal vessels, and subsequently at 1, 3, and 5 min. A Baird Atomic filter with an 80 per cent transmission at 4800 Å and a broad transmission band of 400 Å was used for excitation, and an Ilford 110 Gelatin filter as a barrier.

Blood specimens were obtained from 95 patients who had undergone angiography in 1974. Dr Pauline O'Neill of the Department of Clinical Microbiology, Louis Jenner Laboratories, St Thomas's Hospital, London SE1, performed *Treponema pallidum* haemag-

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glutination (TPHA) tests and Venereal Disease Reference Laboratory (VDRL) slide tests for anticardiolipin antibody on the specimens. Solubility tests for sickle haemoglobin were performed by Professor R. G. Huntsman in the Department of Pathology, Lambeth Hospital, London SE1, and haemoglobin electrophoresis was done by Dr S. Welch in the Department of Biochemistry, London Hospital Medical College, London E1.

Results

Table I shows the age and sex distribution of the 244 patients. Relatively more young males were included in the savanna, but the male/female ratio was the same in both areas (approximately 5:1).

In the 140 savanna patients the pretreatment mean numbers of microfilariae per mg of skin (mf/mg) at the left outer canthus, shoulder, buttock, and calf, were 32, 45, 120, and 95 respectively. In only five of them was the skin concentration less than 50 mf/mg at all four sites; two were old men, one was a boy aged 6 years, and in the other two there was a doubtful history of previous treatment. The savanna patients were thus shown to be heavily infected. Microfilariae were seen in the cornea in 134 of the 140 patients (95·7 per cent). In 22 patients 1–5 microfilariae were present, in 29 6–20, and in 83 more than 20 microfilariae. Microfilariae were also seen in the anterior chamber in 120 patients (85·7 per cent) at a single pre-treatment examination (1–5 microfilariae in 75 patients, 6–20 in 28, and over 20 in 17). Microfilariae were seen in the retrolental space or in the vitreous in 47 of the 140 cases (33·6 per cent).

Valid pre-treatment microfilarial density figures were available from only 52 of the 104 rain-forest patients, and skin snips had not been taken at the outer canthus and calf. The mean number of mf/mg was 42 at the shoulder and 124 at the buttock. Microfilariae were seen in the cornea in 33 of these 52 patients (63·5 per cent), 1–5 in 18 cases, 6–20 in 11, and more than 20 in four. They were seen in the anterior chamber in 46 patients (88·5 per cent), 1–5 in 21, 6–20 in 12, and more than 20 in 13, and in the retrolental space or vitreous in 22 (42·3 per cent).

Table I *Age and sex distribution by area*

	Savanna				*Rain-forest*			
	Males		*Females*		*Males*		*Females*	
Age (yrs)	*No.*	*(Per cent)*	*No.*	*(Per cent)*	*No.*	*(Per cent)*	*No.*	*(Per cent)*
5–9	3	(2)	1	(1)	1	(1)	0	(0)
10–19	41	(29)	7	(5)	8	(8)	3	(3)
20–29	32	(23)	11	(8)	16	(15)	4	(4)
30–39	23	(16)	6	(4)	20	(19)	5	(5)
40–49	8	(6)	5	(4)	26	(25)	5	(5)
50+	3	(2)	0	(0)	16	(15)	0	(0)
Total	110	(79)	30	(21)	87	(84)	17	(16)

Table II *Pattern of ocular disease (shown as a percentage of the population studied)*

		Savanna	*Rain-forest*
Morphology	Retinal pigment epithelial atrophy		
	mild	20·7	25·0
	severe	36·4	40·4
	Atrophy of retina and choriocapillaris	20·7	20·2
	Ill-defined sub-retinal swelling	5·7	5·8
	Subretinal fibrosis	6·4	11·5
Distribution	Temporal	54·3	56·7
	Nasal	7·1	7·7
	Peripapillary	10·0	7·7
Optic nerve disease	Optic atrophy	55·7	67·3
	Pronounced sheathing of vessels	13·6	19·2
	Swelling of optic disc	26·4	11·5

In this selected group there were thus relatively more savanna patients showing microfilariae in the cornea, whereas relatively fewer showed them in the anterior chamber and posterior to the lens.

Since the pattern of posterior segment lesions was similar in both sexes and in treated and untreated patients, the ocular analysis is given by area only. Fundus lesions were analysed in terms of their morphology and distribution, and the relative frequency of the different forms and of the severity of the fundus disease were summarized by area (Table II). The changes in the optic discs were analysed, and the relative contribution to reduction of visual acuity of choroido-retinal and optic nerve lesions was also assessed.

1. CHOROIDO-RETINAL CHANGES

Many of the fundi presented a polymorphic appearance, and it was common to observe lesions of different appearance in the same fundus. Within individual lesions, one part often presented a different appearance from another. The morphology and distribution of the choroido-retinal lesions

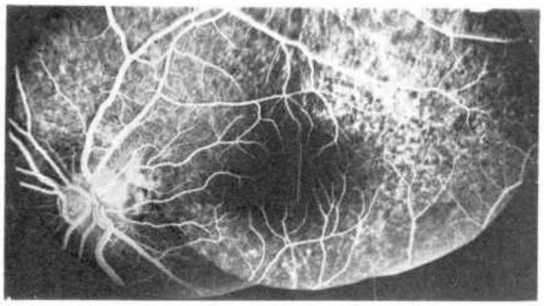


FIG. 1 *Irregular atrophy of pigment epithelium temporal to fovea giving rise to mottled hyperfluorescence during fluorescein fundus angiography*

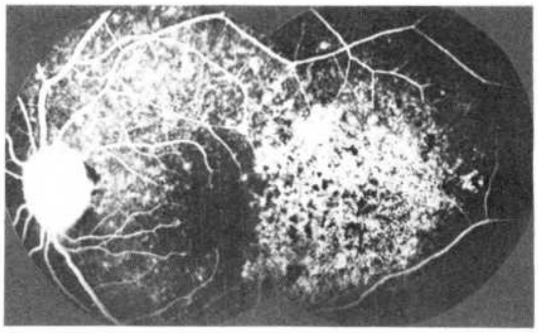


FIG. 2 *Confluent atrophy of pigment epithelium temporal to fovea shown as transmission defect*

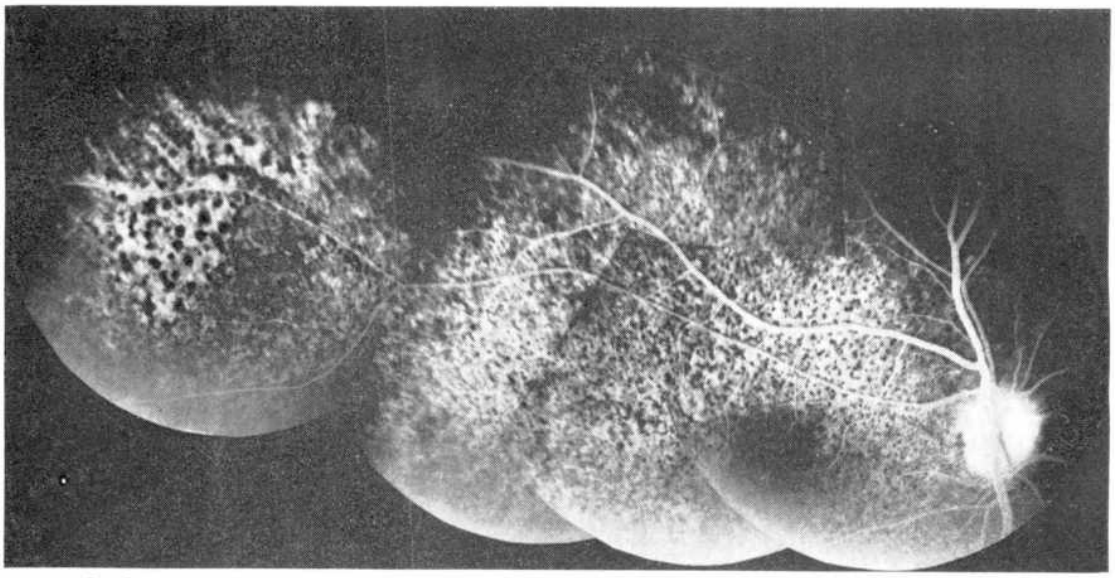


FIG. 3 *Confluent atrophy of pigment epithelium extending from optic disc upper temporally with evenly distributed punctate hyperpigmentation throughout lesion. Leakage of dye from optic disc also occurred*

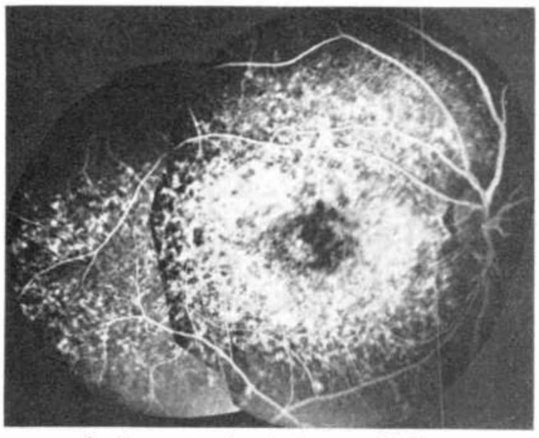


FIG. 4 *Confluent atrophy of pigment epithelium surrounding fovea*

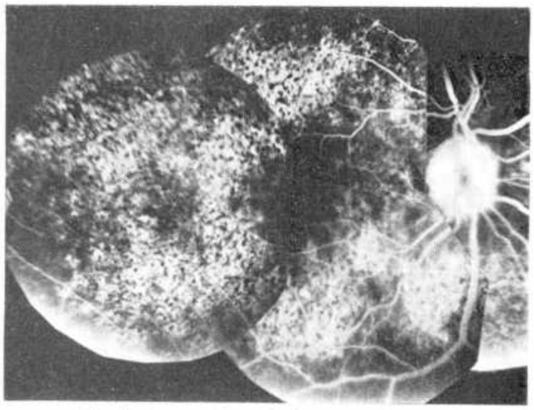


FIG. 5 *Confluent atrophy of pigment epithelium occupying whole of posterior pole with leakage of dye from optic disc*

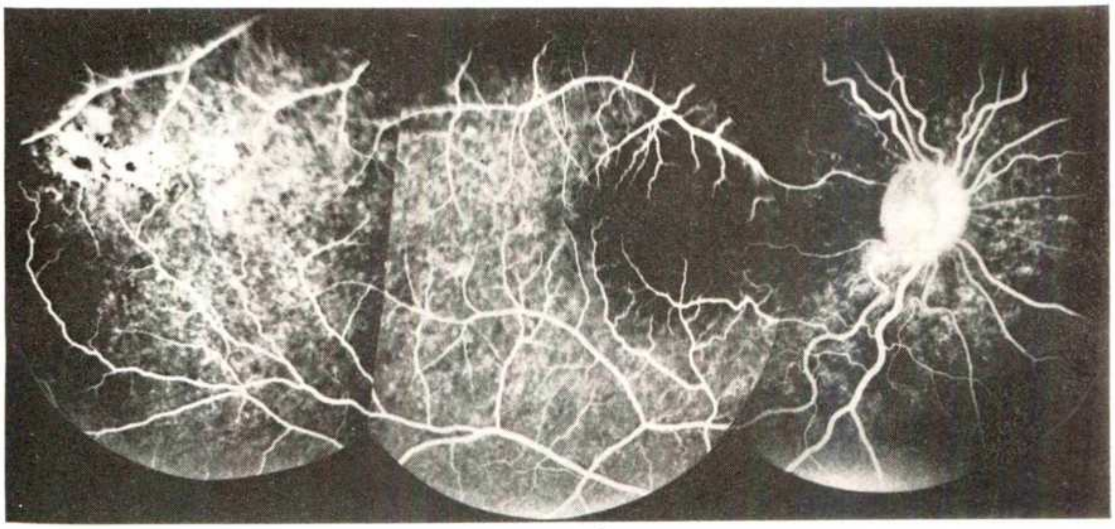


FIG. 6 *Isolated temporal lesion with leakage of dye from optic disc*

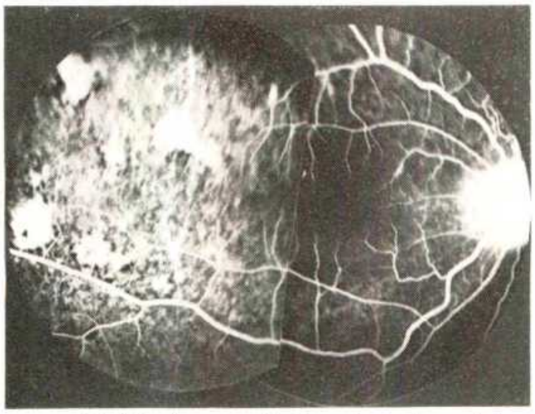


FIG. 7 *Multifocal temporal lesions with leakage of dye from optic disc*

were usually similar in both eyes, but in a few patients striking asymmetry was seen. Widespread disease was not necessarily accompanied by severe morphological change, since in many fundi the entire posterior pole was affected by pigment epithelial atrophy only.

The changes observed in the fundus were as follows:

Morphology

Atrophy of the retinal pigment epithelium

In its mildest form this was represented by an ill-defined area of uneven thinning of the pigment epithelium, which showed mottled hyperfluorescence on fluorescein fundus angiography (Plate 1*a*; Figs 1, 9*a*). This change alone was seen in 55 patients (22·5 per cent), 29 in the savanna and 26 in the rain-forest. It was sometimes difficult to identify by ophthalmoscopy, and fluorescein angiography was used as a confirmatory test whenever possible.

In its more severe form there was a well-defined greyish area of confluent atrophy of the pigment epithelium (Plates 1*b–d*, 2*a*, *b*, *c*, 3*a*, *b*, 4*a*). During the initial transit of dye there was even hyperfluorescence, which faded during the subsequent 10 min (Figs 2–8, 10, 11, 13, 14). This change was seen in 93 patients (38·1 per cent), 51 in the savanna and 42 in the rain-forest.

In 21 patients (14 savanna, seven rain-forest) the lesions were well defined and circular and had a metallic reflex, similar to the tapetal reflex seen in genetically-determined retinal degenerations (Mann, 1937) (Plates 3*a*, *b*; Figs 13*a*, *b*).

Atrophy of the choriocapillaris

This was not seen in isolation, but occurred in areas of pigment epithelial atrophy. Disappearance

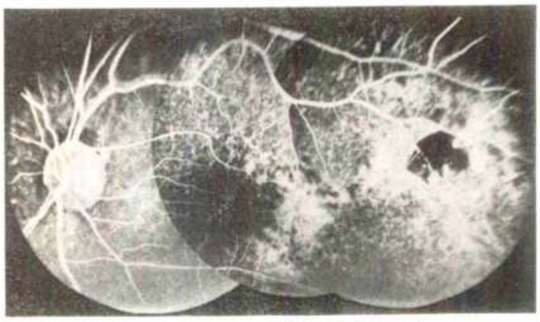
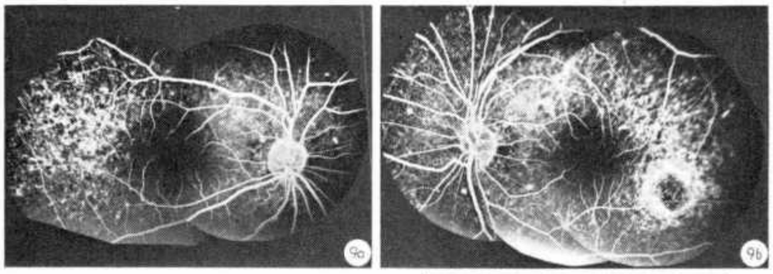


FIG. 8 *Confluent atrophy of pigment epithelium temporal to fovea*



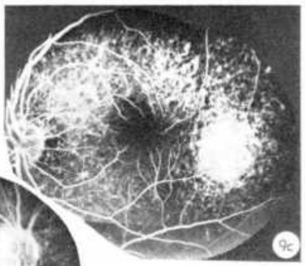


FIG. 9 *Right eye shows irregular pigment epithelial atrophy temporal to fovea* (9a). *Fluorescein angiography of left eye of same patient, illustrated in Plate* 2a, *demonstrated widespread change and focal lesion with atrophy of pigment epithelium and choriocapillaris* (9b). *Five minutes after initial dye entry, central portion was hyperfluorescent* (9c)

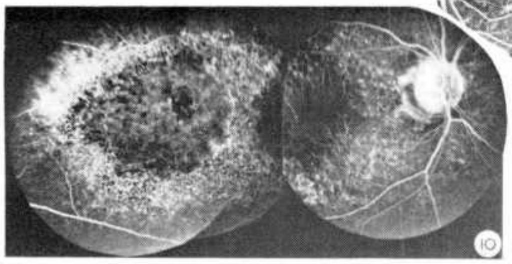


FIG. 10 *Fluorescein angiography of right eye illustrated in Plate* 2b, *demonstrating confluent atrophy of the pigment epithelium temporal to fovea*

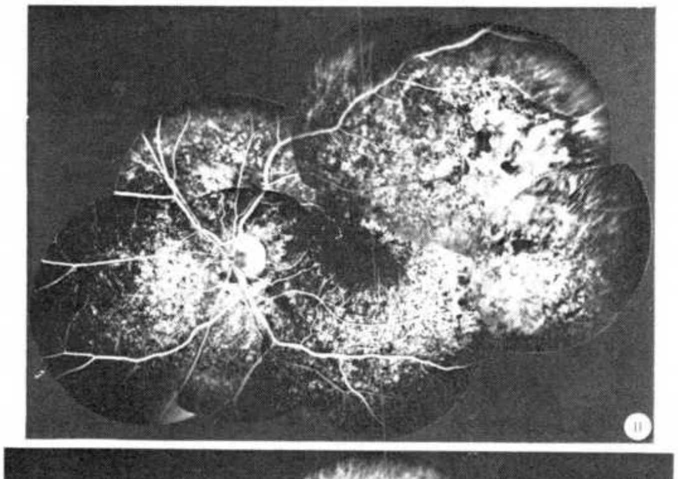


FIG. 11 *Fluorescein angiography of left eye illustrated in Plate* 2c *demonstrating atrophy of pigment epithelium and choriocapillaris temporal to fovea, and widespread atrophy of pigment epithelium only in remainder of posterior pole*

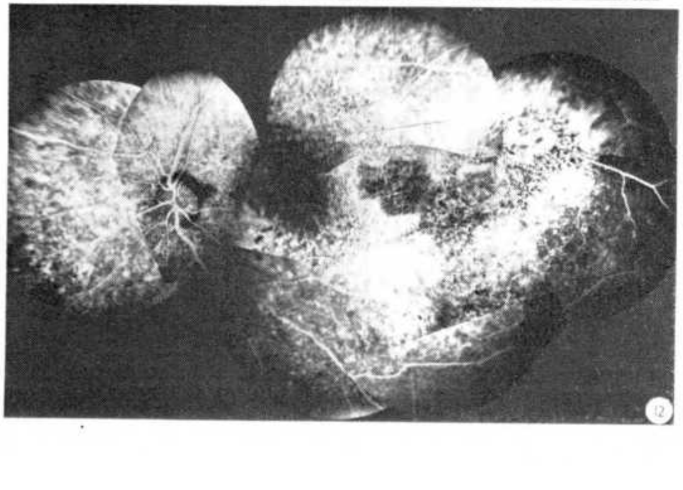


FIG. 12 *Fluorescein angiography of left eye illustrated in Plate* 2d *demonstrating atrophy of pigment epithelium and choriocapillaris temporal to fovea, and widespread atrophy of pigment epithelium only in remainder of posterior pole*

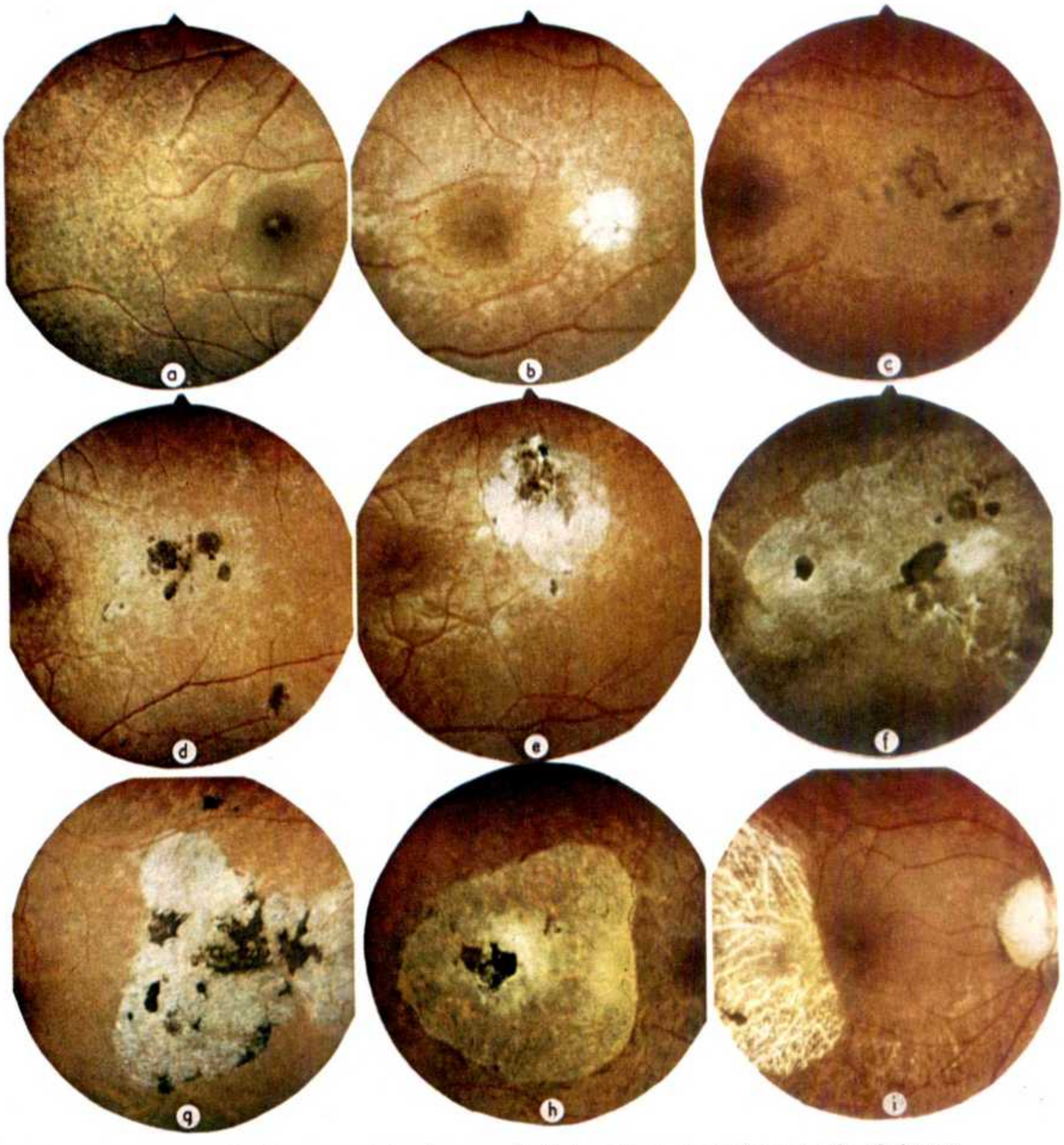
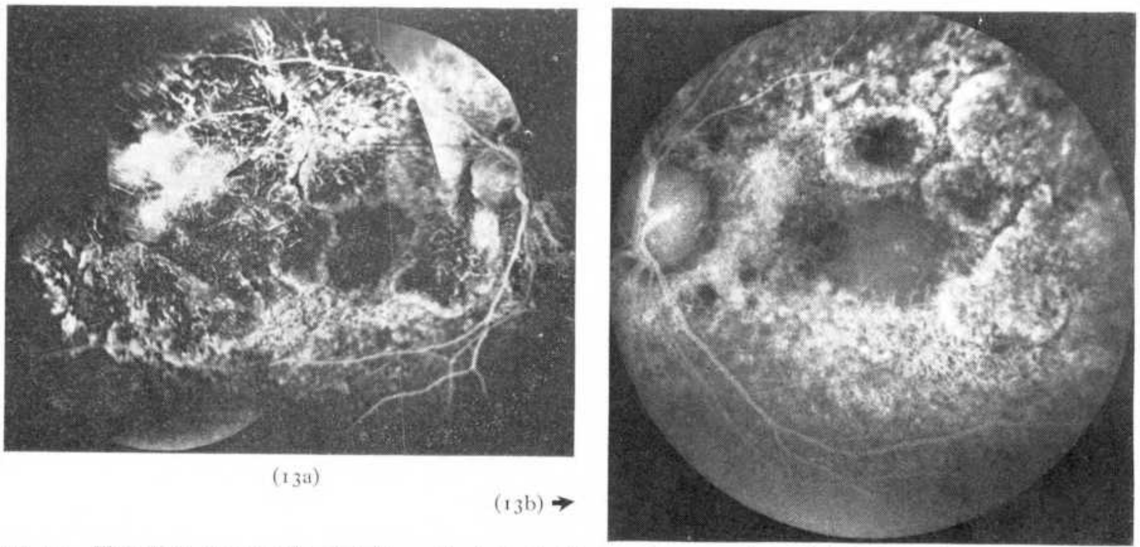


PLATE 1 *Lesions temporal to fovea comprising pigment epithelial mottling* (1a), *confluent atrophy of pigment epithelium* (1b, c, d, e) *and combined atrophy of pigment epithelium and choriocapillaris* (1f, i)

of the choriocapillaris allowed a direct view of the large choroidal blood vessels, which occasionally appeared to be white rather than red (Plates 1*f–i*, 2*a*, 4*a–d*). Fluorescein angiography (Figs 9*b*, *c*, 11, 12, 13*a*, 14–16, 18, 19*a–d*, 20, 21) confirmed closure of the choriocapillaris and showed that all of the large choroidal vessels were patent, indicating that the white appearance was due to thickening of the vessel wall rather than to vessel closure. Atrophy of the choriocapillaris was seen in 50 patients (20·5 per cent), 29 in the savanna and 21 in the rain-forest. Confluent atrophy of the pigment epithelium and choriocapillaris affecting the whole of the posterior fundus was seen in eight patients only (Plate 4*d*; Fig. 20). In large areas of atrophy of this type, islands of surviving choriocapillaris could often be demonstrated by angiography (Fig. 21). This change was most frequently seen in a part of the posterior pole, which was otherwise diffusely diseased (Plates



(13a)

(13b) →

FIG. 13 *Fluorescein angiography of right eye illustrated in Plate* 3a *demonstrating well-defined circular areas of pigment epithelial atrophy throughout posterior pole, but sparing fovea* (13a). *There is atrophy of choriocapillaris above and temporal to fovea with leakage of dye from subretinal fibrous tissue. Left eye of same patient (Plate* 3b) *shows similar disease* (13b)

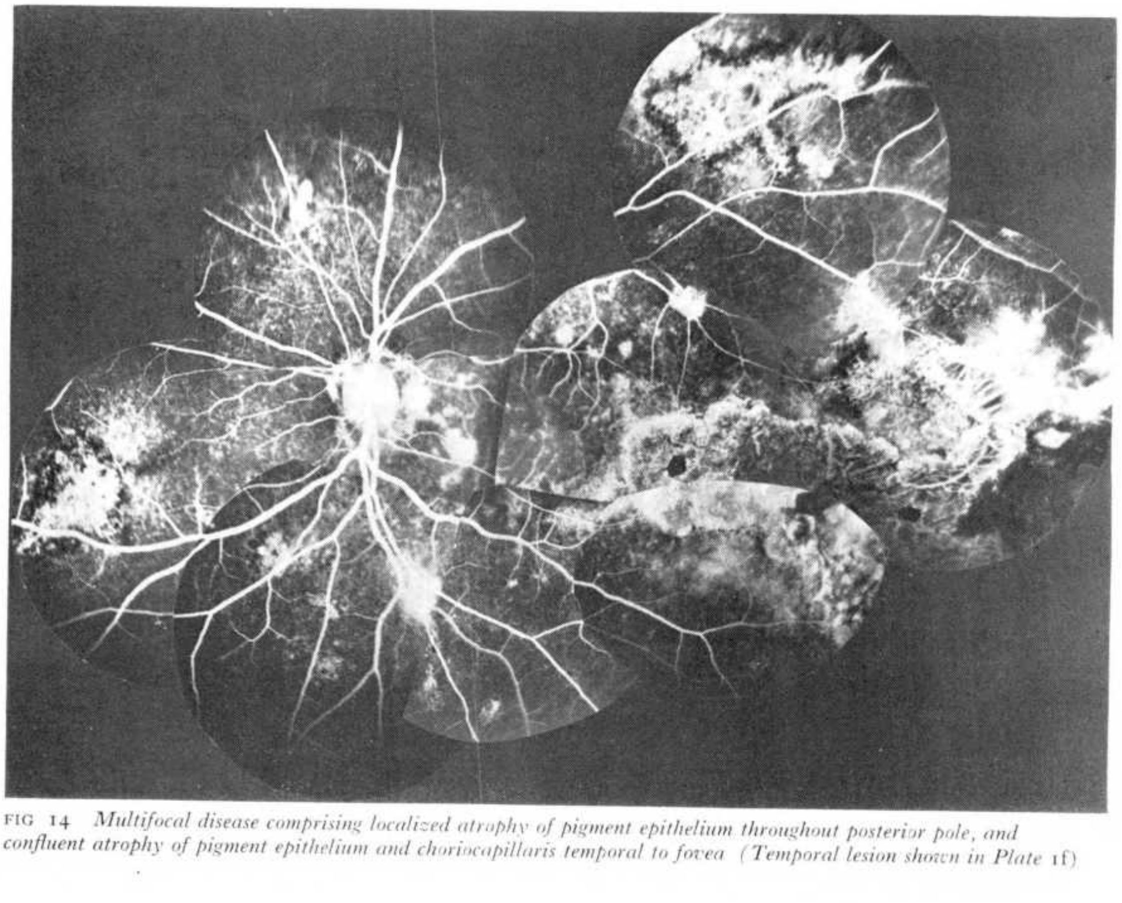


FIG 14 *Multifocal disease comprising localized atrophy of pigment epithelium throughout posterior pole, and confluent atrophy of pigment epithelium and choriocapillaris temporal to fovea (Temporal lesion shown in Plate* 1f)

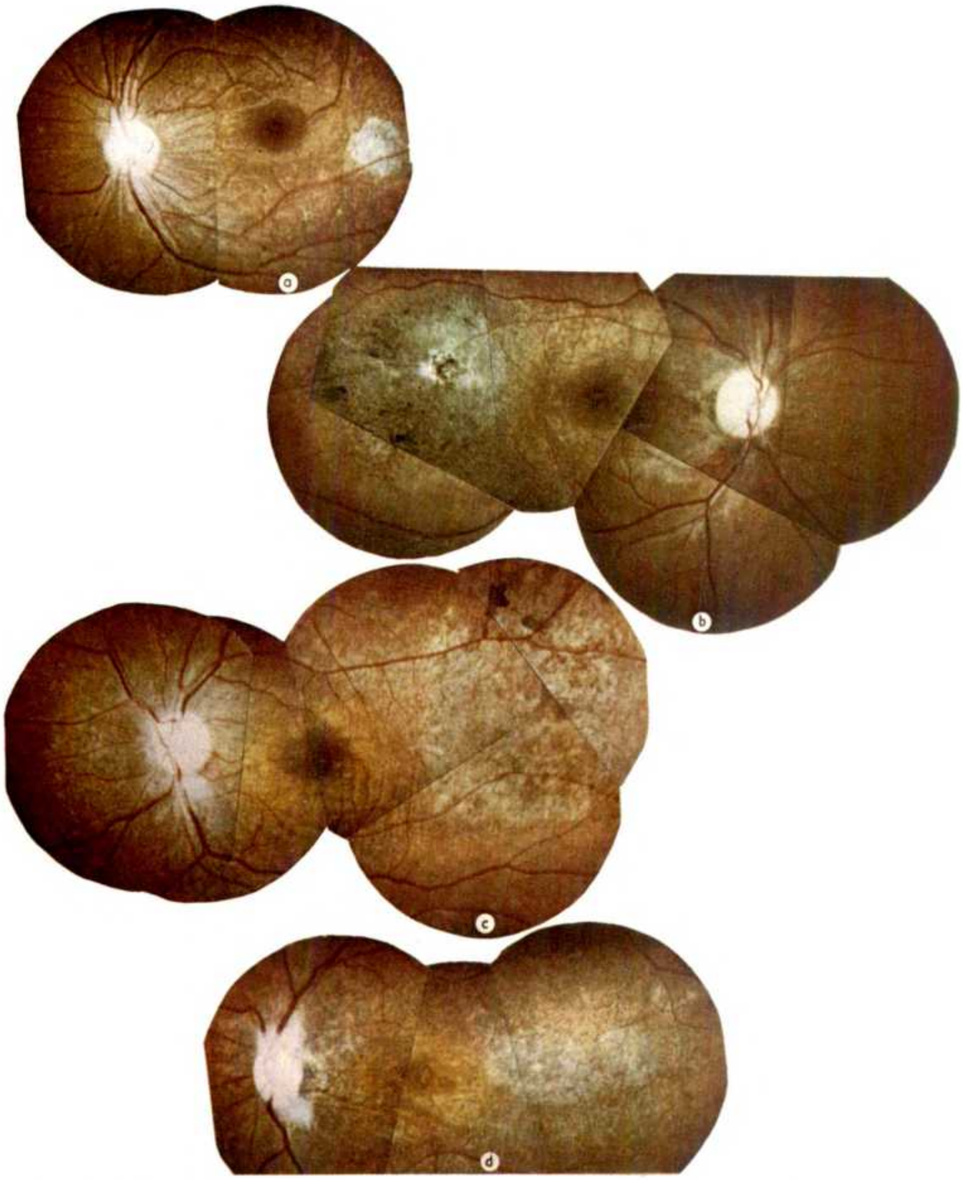


PLATE 2 *Lesions temporal to fovea consisting of confluent atrophy of pigment epithelium* (2a–d). *In one patient* (2d) *there is peripapillary fibrosis*

1*h*, *i*, 2*a*, 3*c*, 4*a*, *b*; Figs 9*b*–*c*, 10–19). These patches were hypofluorescent during the initial transit of dye due to lack of choriocapillaris, but when small became hyperfluorescent after 5 min (Figs 9*b*, *c*).

Ill-defined pale swelling at the level of the choroid and pigment epithelium

Lesions of this type occurred in areas of diffuse disease, and were identified in 14 patients (5·7 per cent) eight in the savanna and six in the rain-forest. Fluorescein angiography showed these lesions to be highly vascular, and after initial dye transit there was progressive leakage of dye into the lesion (Figs 19*a*–*d*, 21).

Subretinal fibrosis with widespread atrophy of the retinal pigment epithelium and choroid

This deep lesion was white with well-defined borders and occurred in 21 patients (8·6 per cent), nine in the savanna and 12 in the rain-forest

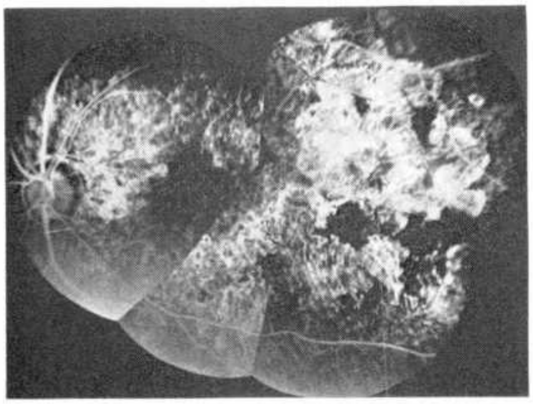


FIG. 15 *Confluent atrophy of pigment epithelium and choriocapillaris temporal to fovea*

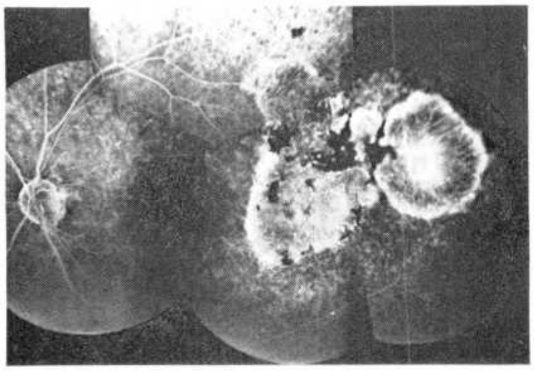


FIG. 16 *Confluent and well-defined atrophy of pigment epithelium and choriocapillaris temporal to fovea*

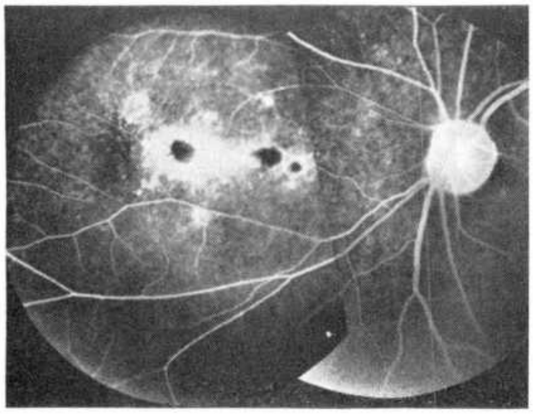


FIG. 17 *Isolated nasal lesion comprising confluent atrophy of pigment epithelium*

(Plates 3*a*–*d*). Fluorescein angiography indicated the presence of capillaries within the fibrous tissue (Figs 13*a*, 16, 21).

Hyperpigmentation at the level of the pigment epithelium

This was common to all forms of atrophy of the retinal pigment epithelium and choriocapillaris, and was never seen in isolation. It presented as brown or mauvish-brown spots or discs, uniformly distributed throughout the area of choroido-retinal atrophy (Plate 1*c*; Figs 2, 3, 4, 5), or as irregular hyperpigmentation in any part of the lesion (Plates 1*d*–*i*, 2*b*–*d*, 3*a*–*d*, 4*a*–*b*; Figs 6–8, 10–18). In two patients the changes were widespread, and gave rise to the appearance of pigmentary retinopathy (pseudoretinitis pigmentosa). On fluorescein angiography the pigment obscured the background choroidal fluorescence.

Pigment migration forwards into the retina was relatively uncommon. It presented as solid-black masses, or more rarely as 'bone corpuscle' and retinal paravascular pigmentation.

Posterior retinal oedema and uveitis

In three patients who had severe uveitis with a cellular reaction in the aqueous and vitreous humours, the posterior retina was oedematous. On fluorescein angiography there was dye leakage into the retina from the retinal capillaries and veins (Figs 22*a*, *b*, *c*).

Distribution

The most common site of fundus disease was temporal to the fovea (Plates 1*a*–*i*, 2*a*–*d*, 3*b*–*d*, Figs 1–2, 6–10, 12, 13*b*, 15, 16, 18). Lesions at this site were seen in 135 patients (55·3 per cent), 76 in the savanna and 59 in the rain-forest. Isolated lesions nasal to the optic disc were relatively less common, presenting in only 18 patients (7·4 per cent), 10 in the savanna and eight in the rain-forest (Plate 4*a*; Figs 17, 18). Marked peripapillary pigmentary atrophy was seen in 22 patients (9·0 per cent), 14 in the savanna and eight in the rain-forest. While some patients had isolated lesions at these sites, others had multiple well-defined lesions in the posterior fundus which frequently formed an interrupted ring around the macular region (Fig. 14). The entire posterior pole was involved in 63 patients (25·8 per cent), 36 in the savanna and 27 in the rain-forest (Plates 3*c*, 4*b*–*d*, Figs 4, 5, 11–13*a*, 19–21). In 38 of them (22 in the savanna and 16 in the rain-forest), the macular region was spared (Plates 3*a*, *c*, 4*c*; Figs 4, 5, 13*a*, 19*a*).

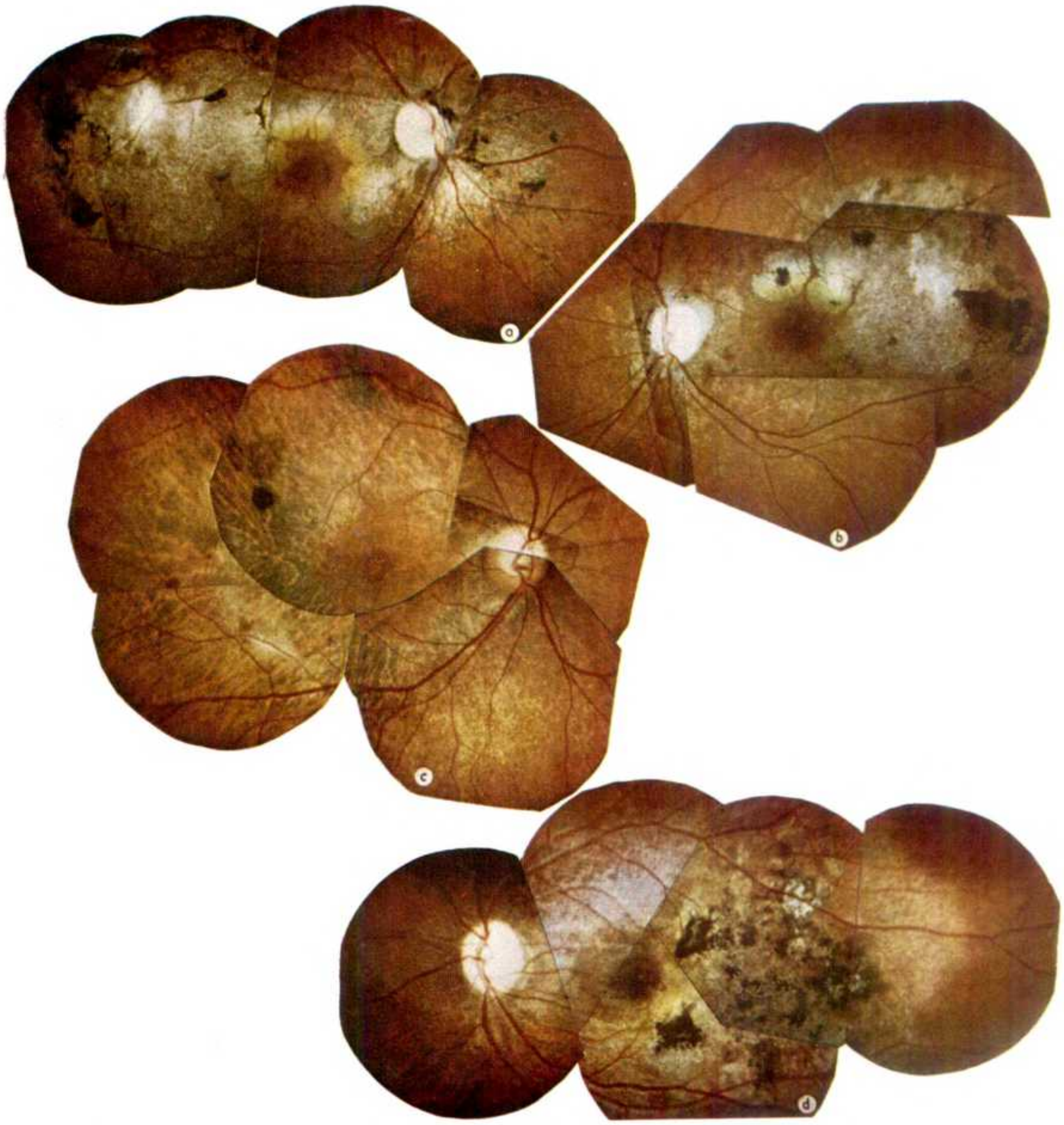


PLATE 3 *Widespread confluent atrophy of pigment epithelium occurring as well-defined lesions* (3a, b), *as diffuse atrophy occupying whole of posterior pole but sparing macula* (3c[illegible] *temporal region associated with marked hyperpigmentation* (3d). *In all four patients there was localized subr*[illegible] *fibrosis*

2. OPTIC DISC CHANGES

Optic atrophy was present in 148 patients (60·6 per cent), 78 in the savanna and 70 in the rain-forest. In each case retinal nerve fibre loss was indicated by defects in the superficial retinal white reflex, and baring of the retinal blood vessels was apparent (Hoyt, Frisen, and Newman, 1973) (Fig. 23). Pronounced sheathing of the major retinal vessels on the optic disc and extending 1 to 2 disc diameters away from the disc was present in 39 of these patients (19 in the savanna and 20 in the rain-forest) (Plate 2*d*; Fig. 26), and in three there was marked peripapillary hyperpigmentation.

In 137 (92·6 per cent) of the patients with optic atrophy there were associated choroido-retinal changes compatible with onchocerciasis, but in most of these the fundus changes were mild and it was unlikely that the atrophy was consecutive to

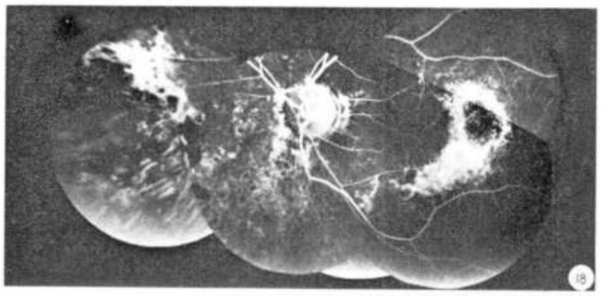


FIG. 18 *Fluorescein angiography of left eye illustrated in Plate* 4a *demonstrating focal lesions temporal and nasal to fovea comprising atrophy of pigment epithelium and choriocapillaris*

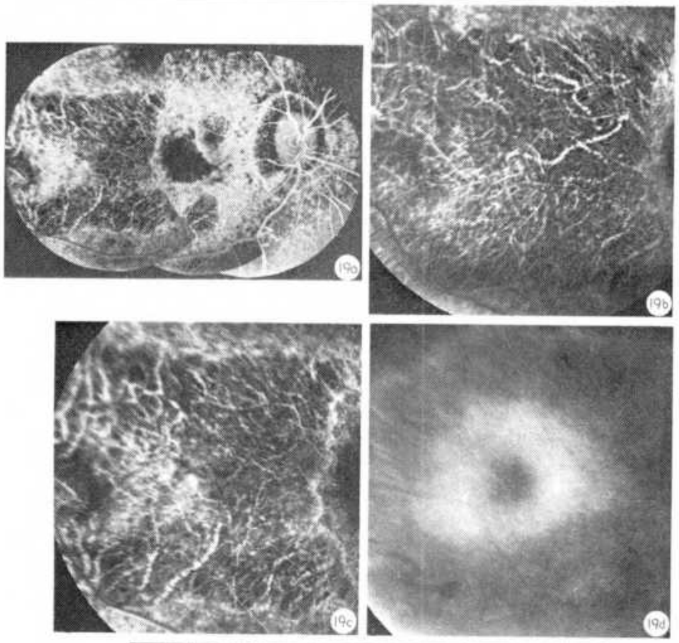


FIG. 19 *Fluorescein angiography of right eye illustrated in Plate* 4b *demonstrating combined atrophy of pigment epithelium and choriocapillaris temporal to fovea, and confluent atrophy of pigment epithelium elsewhere in posterior pole but sparing macula* (19a). *Central part of this area had subretinal vascular lesion* (19b, c) *from which there was profuse leakage of dye* (19d)

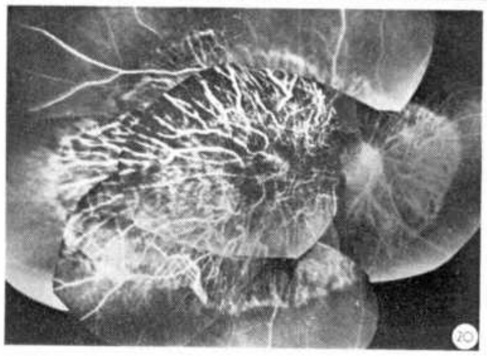


FIG. 20 *Fluorescein angiography of right eye illustrated in Plate* 4d *demonstrating confluent atrophy of pigment epithelium and choriocapillaris throughout posterior pole*

retinal disease. By contrast, severe choroido-retinal atrophy affecting the entire posterior pole was seen without optic atrophy in nine patients.

Swelling of the optic disc was seen in 49 patients (20·1 per cent), 37 in the savanna and 12 in the rain-forest, of whom 29 had choroido-retinal lesions compatible with onchocerciasis. Fluorescein angiography was performed in 37 of these cases and this showed dilatation of the superficial capillaries of the optic disc and peripapillary retina, with leakage of dye into the nerve head (Figs 1, 3, 5–7, 10, 11, 24, 25).

3. VISUAL FUNCTION

The visual acuity of each eye is shown for savanna and rain-forest patients separately in Table III.

Many patients had good central vision, and the

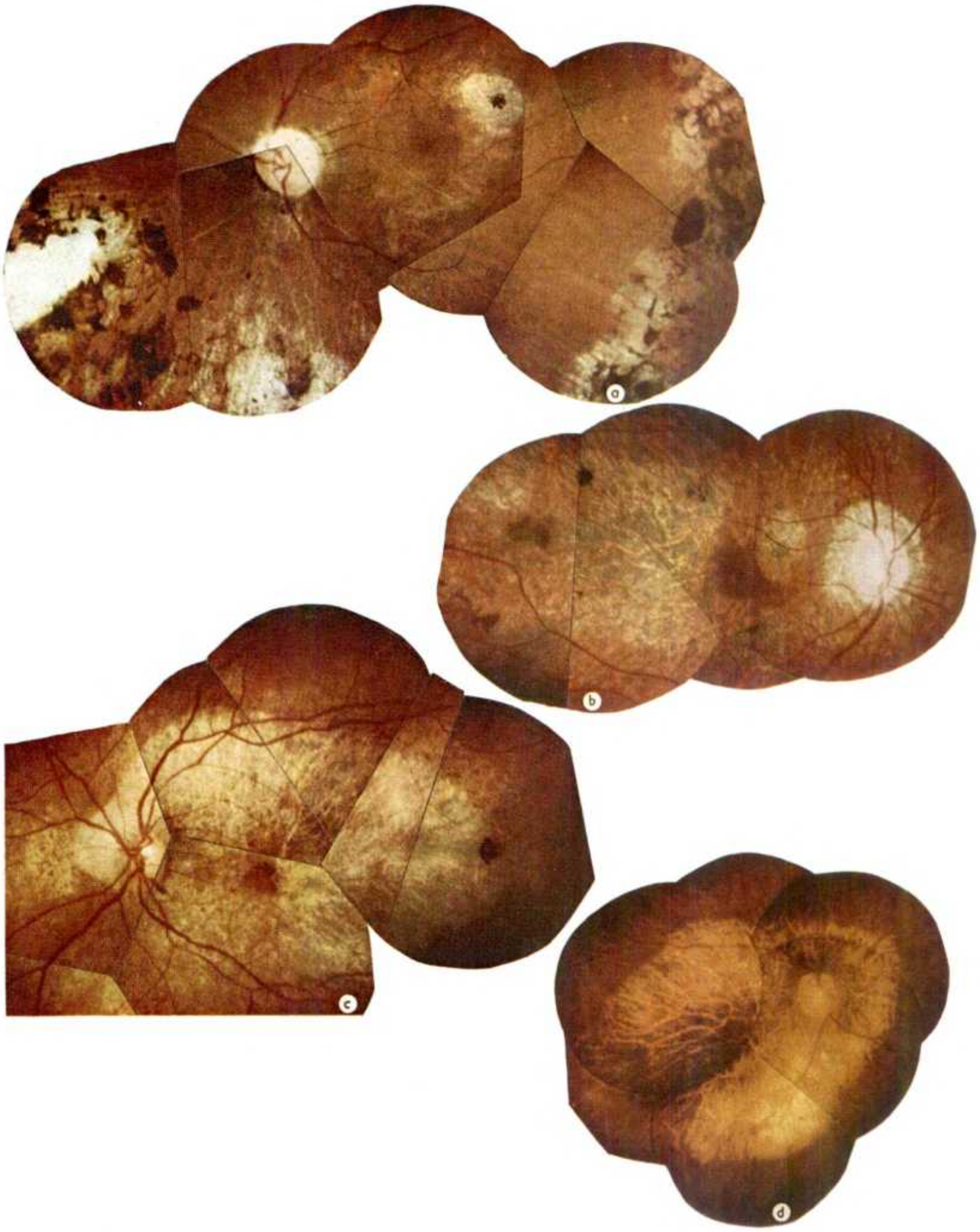


PLATE 4a *Widespread focal disease in which temporal lesion consists of confluent atrophy of pigment epithelium and nasal lesion shows combined atrophy of pigment epithelium and choriocapillaris*

b *Confluent atrophy of pigment epithelium and choriocapillaris temporal to macula. Within this area there is vascular subretinal lesion*

c *Confluent atrophy of pigment epithelium occupying whole of posterior pole but sparing macula and accompanied by atrophy of choriocapillaris temporally and superiorly*

d *Confluent atrophy of pigment epithelium and choriocapillaris affecting whole of posterior pole*

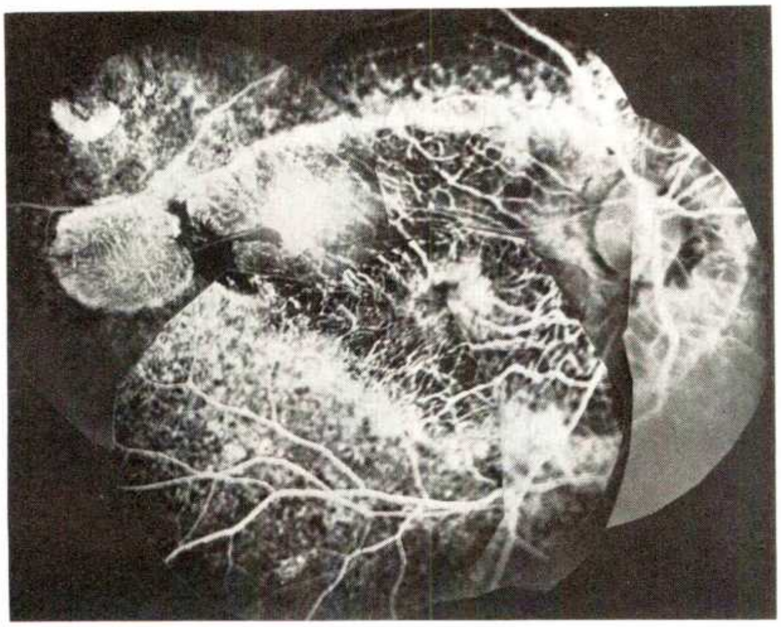


FIG. 21 *Fluorescein angiography demonstrating confluent atrophy of pigment epithelium and choriocapillaris throughout the posterior pole except in temporal part of lesion where choriocapillaris survives. Within area is subretinal vascular lesion with dye leakage*

median visual acuity in each group was 6/12. However, it must be emphasized that most patients had symptoms related to visual field loss and poor night vision, and on examination were found to have very restricted visual fields, so that many with good central visual acuity were severely handicapped.

Table III *Visual acuity by area*

Visual acuity	*Savanna*				*Rain-forest*			
	Right eye		*Left eye*		*Right eye*		*Left eye*	
	No.	*(Per cent)*	*No.*	*(Per cent)*	*No.*	*(Per cent)*	*No.*	*(Per cent)*
6/6	56	(40)	53	(38)	34	(33)	36	(35)
6/9	12	(9)	11	(8)	16	(15)	13	(12)
6/12	15	(11)	23	(16)	7	(7)	3	(3)
6/18	9	(6)	7	(5)	6	(6)	5	(5)
6/24	6	(4)	3	(2)	5	(5)	9	(9)
6/36	3	(2)	7	(5)	3	(3)	1	(1)
6/60	2	(2)	3	(2)	2	(2)	4	(4)
Counting fingers	8	(6)	9	(6)	3	(3)	7	(7)
Hand movements	12	(9)	12	(9)	11	(11)	11	(11)
Perception of light								
Present	9	(6)	3	(2)	2	(2)	6	(6)
Absent	8	(6)	9	(6)	15	(14)	9	(9)
Total	140		140		104		104	

Altogether 145 patients (59·4 per cent) had either very poor vision in both eyes, or the visual field was restricted to within 5° of fixation in the better eye, so that they were severely handicapped. It was considered that in 127 of these (87·6 per cent) the visual loss was determined by optic nerve rather than choroido-retinal disease.

The pattern of visual loss in most patients suggested optic nerve disease. Patients with optic disc swelling were occasionally asymptomatic, but usually complained of visual field loss and poor night vision. In all patients with mild or early disease arcuate defects could be demonstrated. In all cases of established optic nerve disease, whether swelling or atrophy, there was restriction of the visual fields to within 5° of fixation. Five patients had normal optic discs despite a history of recent loss of visual acuity and demonstrable arcuate defects.

4. BLOOD TESTS

The results of tests for treponemal disease on the 87 blood samples suitable for testing are shown in Table IV. It is likely that the positive VDRL slide tests in the presence of negative TPHA tests represented a biologically false positive result, so that there was evidence of treponemal infection in 26 patients from the rain-forest but only one in the savanna. Table V shows the type of ocular disease compared with the results of treponemal tests in the patients from the rain-forest, and demonstrates that there was no correlation between the two.

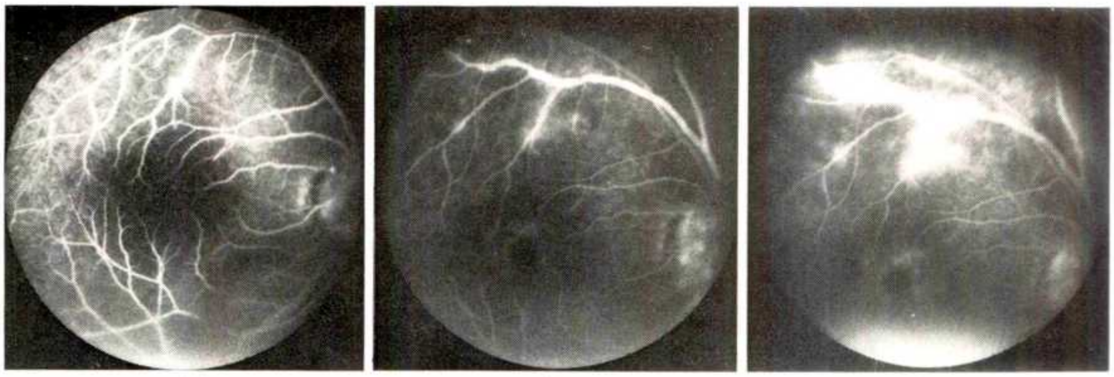

(a) (b) (c)

FIG. 22 *Fluorescein angiography of patient with vitritis and posterior retinal oedema, demonstrating leakage from retinal veins*

Only eight specimens out of the total of 93 suitable for testing had positive solubility tests for sickle haemoglobin (five from the savanna and three from the rain-forest), and electrophoresis showed all eight to contain haemoglobin S and A.

Table IV *Results of tests for treponemal disease*

Treponema pallidum *haemagglutinin assays*	*Venereal Disease Reference Laboratory flocculation tests*	*Savanna*	*Rain-forest*
+	+	0	9
+	−	1	17
−	+	2	2
−	−	40	16
		43	44

Table V *Results of test for treponemal disease compared with type of ocular disease*

Treponema pallidum haemagglutinin	+	+	−	−
Venereal Disease Reference Laboratory	+	−	+	−
1 No fundus disease	0	2	0	3
2 Fundus disease alone				
a mild	2	4	1	2
b severe	1	1	0	0
3 Optic nerve disease alone	2	0	0	3
4 Optic nerve disease with				
a mild fundus disease	2	6	1	5
b severe fundus disease	2	4	0	3

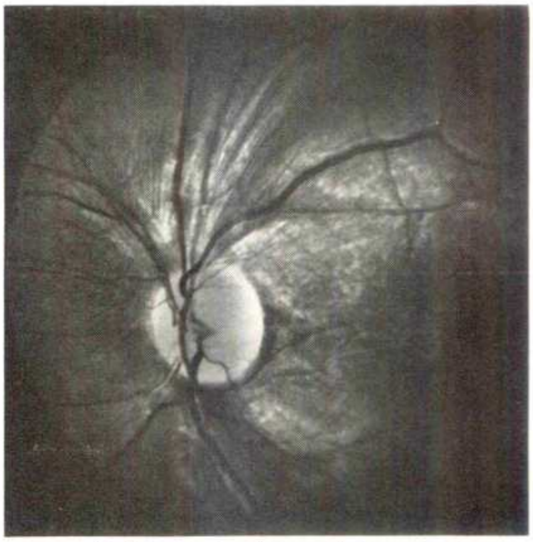
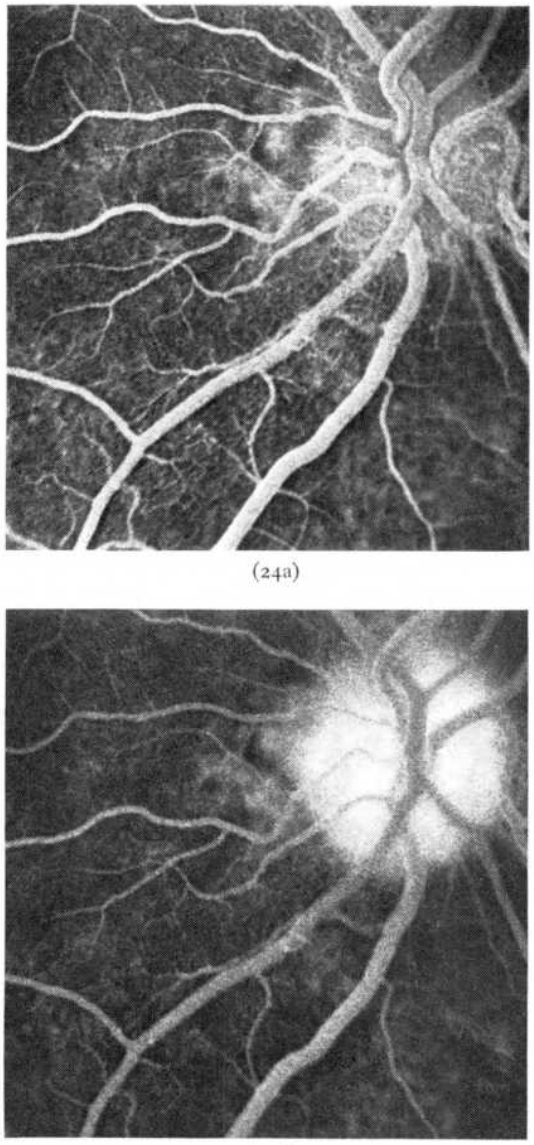


FIG. 23 *Red free fundus photograph demonstrating linear defects in superficial reflex of retina indicating nerve fibre bundle loss*

Fundus changes attributable to sickle cell disease were not seen in this study.

Discussion

The evidence that the posterior segment ocular lesions described in this paper are due to onchocerciasis is largely epidemiological. In the past, various workers have attempted to classify the fundus lesions of onchocerciasis into distinct clinical entities on the basis of their morphology. The best known form of the disease, consisting of well-defined atrophy of the choroid and retina, was first described by Hissette (1932) in the Congo basin and later by Bryant (1935) in Sudan. Ridley


(24a)

(24b)

FIG. 24 *Dilatation of pre- and peripapillary blood vessels* (24a) *and leakage of dye into optic disc* (24b)

(1945) gave the most detailed early account of this lesion in patients from West Africa, and he was not in doubt that the ocular disease was due to infection by *O. volvulus*. On the basis of his own observations and previously published histological material (Hissette, 1932; Bryant, 1935; Semadini, 1943), he thought it likely that the vascular atrophy in the choroid was due to occlusion of short ciliary blood vessels by endarteritis rather than to inflammation in the choroid. However, Neumann and Gunders (1973), in a histopathological study of an eye with the typical changes described by Ridley, found all but one short ciliary artery supplying the diseased area to be normal. The one remaining vessel was markedly narrowed and surrounded by plasma cell infiltration, and they implied that arterial occlusion was unlikely to be important in the pathogenesis of the atrophic lesion.

Rodger (1957, 1960) distinguished two types of fundus lesion in onchocerciasis: an atrophic type, in which signs of inflammation were absent and microfilariae were not seen in the eye, and an inflammatory type, in which abundant microfilariae could be identified. He suggested that vitamin-A deficiency was important in the pathogenesis of the former.

The lack of evidence of vitamin-A deficiency in the present study is in agreement with the findings of Lagraulet (1972). Further, Neumann and Gunders (1963) found microfilariae in the anterior chamber in all patients with the atrophic lesion in Liberia, and our experience in this study supports their observations. Finally, Neumann and Gunders (1973) in their histological study found microfilariae of *O. volvulus* in the choroid at the site of atrophy.

Choyce (1958) described a disease characterized by atrophy of the retina and choroid affecting the whole of the fundus, which he thought was different from choroido-retinitis due to onchocerciasis. These patients were seen at Bonjongo, a village on Mount Cameroon, which he considered to be an isolated community, and he suggested that the disease was genetically determined, since its morphology resembled generalized choroidal atrophy previously described by Sorsby (1939, 1955). However, most authors (D'Haussy, Le Breton, Aubry, Vandendorpe, Lagraulet, Budden, Bisley, and Quarcoopome, 1958; Lagraulet, 1958; D'Haussy and Uemura, 1960; Quéré and others, 1963) have been unconvinced by Choyce's claim that he was describing a disease different from onchocerciasis, and have assumed that the condition described in Bonjongo was a severe form of that described in Africa by Hissette (1932), Bryant (1935), and Ridley (1945), and in Central America by Quevedo (1941) and Clark (1947). We examined a large number of patients on Mount Cameroon, including many from the village of Bonjongo, and saw no condition, even in the blind, which was distinguishable from fundus disease attributable to onchocerciasis.

Quéré and others (1963) recognized three distinct morphological entities (atrophy of the retinal pigment epithelium and choroid, inflammatory choroido-retinitis, and pigmentary retinopathy) and they accepted that onchocerciasis alone could

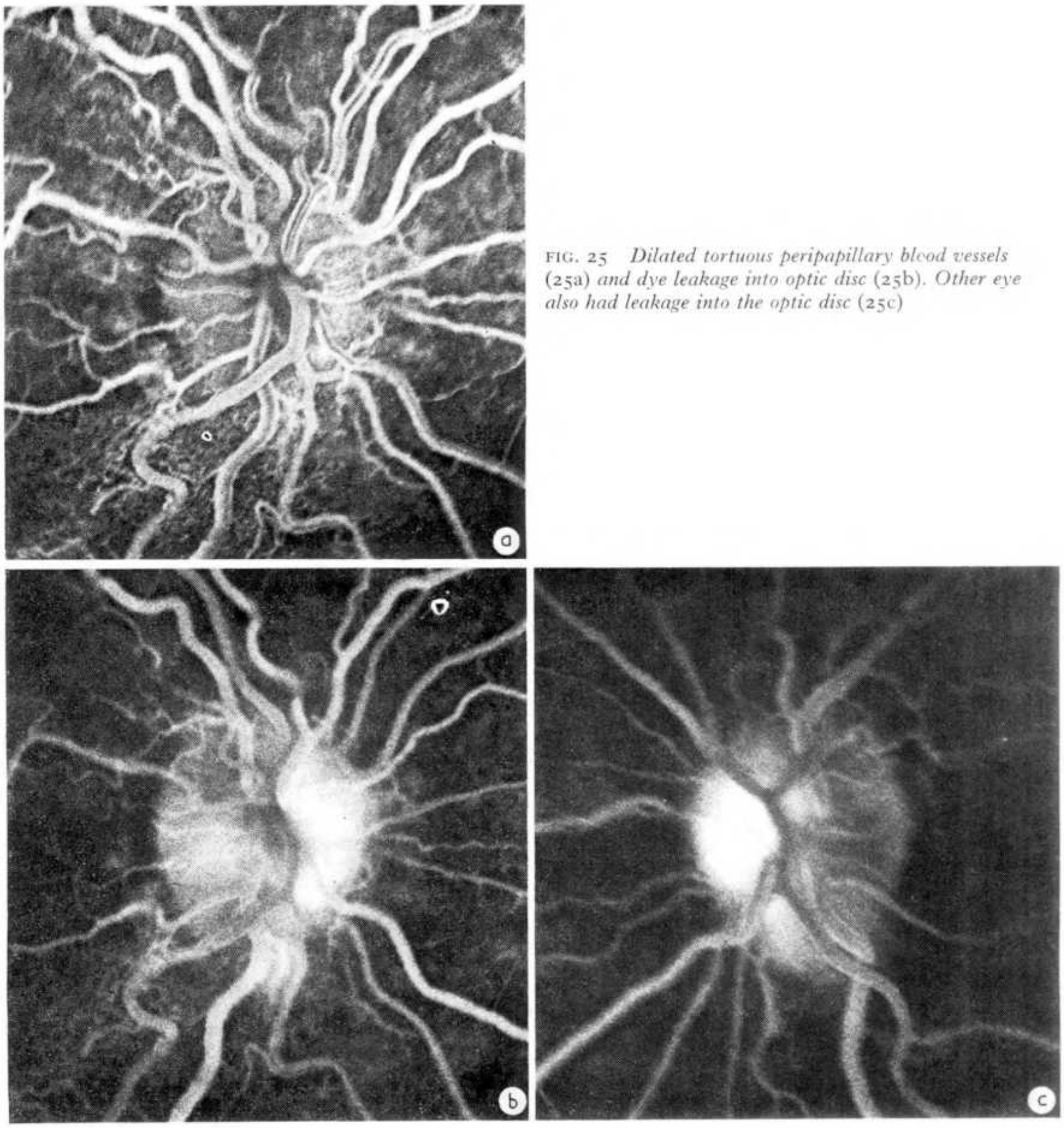


FIG. 25 *Dilated tortuous peripapillary blood vessels* (25a) *and dye leakage into optic disc* (25b). *Other eye also had leakage into the optic disc* (25c)

produce all three disease patterns. Metge, Chovet, Casenave, and Loréal (1974) used fluorescein fundus angiography to study the morphology of lesions in patients with onchocerciasis and they subdivided the changes into specific categories. They accepted that the different types of lesions were all due to onchocerciasis and thought that they represented different stages of severity of the disease.

In the present study, atrophy of the pigment epithelium appeared to be the mildest form of the disease, and in some cases it could be recognized with certainty only by fluorescein fundus angiography. Although the histopathology of this lesion has never been studied, its co-existence with advanced choroido-retinal atrophy elsewhere in the same eye, or in the fellow eye, suggests that it is a mild or early form of the more commonly-described lesion characterized by confluent atrophy of the pigment epithelium and choriocapillaris.

The pale, ill-defined, swollen choroidal lesions, which proved to be vascular and showed leakage of fluorescein, are likely to be choroidal granulomata. The fact that they were seen in areas of choroido-retinal atrophy supports the view that this type of atrophy is the result of inflammation

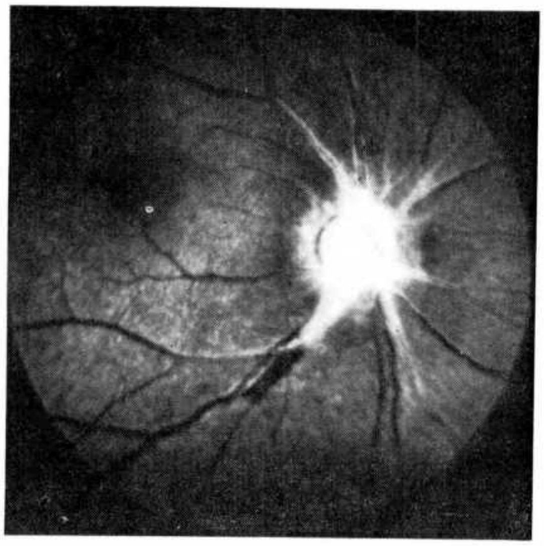


FIG. 26 *Red free photograph illustrating perivascular fibrosis of optic disc*

rather than being genetically determined (Choyce, 1958). It should be pointed out that this inflammatory lesion could be recognized by ophthalmoscopy only with difficulty. Likewise, subretinal fibrosis probably results from scarring following a similar inflammatory lesion, in which invasion of the granuloma by blood vessels is prominent. The well-demarcated grey disc-shaped areas of pigment epithelial atrophy probably represent the site of previous inflammation, albeit less severe than in the vascular lesions.

Unlike Quéré and others (1963) and Metge and others (1974), we were unable to distinguish distinct forms of the disease. From the morphological standpoint, there appeared to be a continuous spectrum from mild to severe disease without any indication of demarcation between one form and another. The heterogeneity of the lesions, and the occurrence of different types of lesion in a single eye, or in the two eyes, strongly suggest that inflammation alone is responsible for the pathogenesis of fundus changes in onchocerciasis. Although the paucity of pigment-containing cells in the retina and the preservation of the outer choroid are both uncharacteristic of most postinflammatory lesions due to other infective agents, these features may be determined by the relatively low antigenicity of the microfilariae of *O. volvulus*. This would result in a low grade and localized inflammatory response associated with little necrosis, analogous to the skin changes in onchocerciasis (World Health Organization, 1974).

The severity of fundus disease in the savanna was similar to that in the rain-forest, and the different types of lesion were seen with the same frequency in both areas (Table II). This is in contrast to the pattern of lesions seen in the cornea, where the blinding sclerosing keratitis is virtually confined to the savanna. Duke and Anderson (1972) showed that microfilariae of the Sudan-savanna strain were more pathogenic to the rabbit cornea than microfilariae of the rain-forest strain, but the present study revealed no evidence of varying pathogenicity to the human fundus.

The constancy of the distribution of choroidoretinal changes in onchocerciasis is striking, and it was recognized by Budden (1973) and Metge and others (1974) that the lesions overlie the site of scleral perforation of the long ciliary arteries. Lesions temporal to the fovea, seen in 135 patients in this series, corresponded to the site of entry of the temporal long ciliary artery, and although lesions overlying the entry of the nasal long ciliary artery occurred, they were far less common (18 patients). The ring of involvement in the posterior pole with sparing of the macula, which occurred in more severe disease, overlies the ring of entry of the short ciliary arteries. The significance of this distribution could be easily understood if the microfilariae passed from the peribulbar orbital tissue into the choroid through the scleral canals as was indicated by Neumann and Gunders (1973), although the disparity between isolated temporal and nasal lesions would have to be explained. If the source of microfilariae was adult worms in the temporal region and the microfilariae gained access to the orbit through its temporal margin, it is likely that their concentration in the temporal side of the orbit would be higher than in the nasal side. It would follow that penetration by microfilariae through the temporal scleral canals would occur with greater frequency than through the canals on the nasal side. However, it has also been shown that the prevalence of *O. volvulus* microfilariae in the blood is high in heavily infected persons (Fuglsang and Anderson, 1974). If the organism causes disease by entering the eye *via* the blood stream, the distribution of the choroidoretinal lesions remains unexplained.

That optic nerve rather than choroido-retinal disease may be the cause of visual loss in onchocerciasis has been well recorded. Most authors agree that the optic nerve disease is inflammatory in origin, and microfilariae have been demonstrated in optic nerve tissue (Giaquinto Mira, 1934; Rodger, 1960; Paul and Zimmerman, 1970). During the active stage the nerve head is swollen (Védy and Sirol, 1971), and it later becomes atrophic with ill-defined margins and perivascular sheathing and pigmentation. D'Haussy, Boyer, and Aubert (1963) described one case in detail.

The patient had a severely restricted visual field in one eye, altitudinal loss in the other, and poor dark adaptation in both. The electroretinogram was normal or near normal in both eyes, indicating lack of involvement of the outer retina.

Patients with optic nerve disease and a short history of visual field loss had easily demonstrable arcuate field loss, and in some the field was restricted to the central 5°. It is likely that the symptom of poor night vision, which is so common in patients with ocular onchocerciasis, is due in many cases to denervation of the rod-rich peripheral retina by optic nerve disease, rather than to retinal disease to which it has been almost universally ascribed. The pattern of optic nerve disease was very similar to that seen in syphilis. However, there was no correlation between the results of serological tests for treponemal infection and the type of ocular disease. Positive serological tests were found almost exclusively in patients from the rain-forest, whilst the optic nerve disease was found with equal frequency in the two groups. That the optic nerve disease is not due to syphilis is in agreement with the conclusion of D'Haussy, Pfister, Rit, and Breteau (1957) drawn from a study in Mali.

In the past, little attention has been paid to the relative importance of optic neuritis and choroido-retinitis as blinding conditions in patients with posterior segment ocular disease caused by *O. volvulus* infection. D'Haussy and others (1954) found isolated optic nerve disease in 5 per cent of 536 patients suffering from ocular onchocerciasis in Bamako, and Weyts (1956) reported a frequency of 7 per cent in patients in Zaire. A further 31 per cent of Weyts's patients had combined optic nerve disease and choroido-retinitis, but no assessment was made of the relative significance of the two lesions as a cause of visual loss.

In this study, the frequency of optic nerve disease as the cause of blindness (87·6 per cent) was striking. This is particularly important since optic nerve disease can cause severe and progressive visual loss leading to irretrievable blindness in early life. More than a quarter of the patients in our series were under the age of 20 years, and blindness from posterior segment disease due to onchocerciasis is not uncommon in heavily infected persons at that age. This contrasts with previous views (Lagraulet, 1972).

Summary

Posterior segment ocular lesions were examined in 244 selected patients with onchocerciasis from the Sudan-savanna and rain-forest areas of the United Cameroon Republic. Fluorescein fundus angiography was performed on 210 cases.

As a result of this study the following conclusions were drawn:

1. The heterogeneity of single lesions, and the occurrence of different types of lesion in a single eye or two eyes, prevented subdivision of the disease into distinct forms and suggested that inflammation alone was responsible for fundus lesions in onchocerciasis.
2. Optic nerve disease, alone or in the presence of choroido-retinal changes, was responsible for a large proportion of the blindness due to posterior segment lesions in onchocerciasis (87·6 per cent in this series).

We should like to thank Professor G. S. Nelson and Dr B. O. L. Duke for helpful criticism, and we acknowledge the help of our assistants in the United Cameroon Republic, Mr S. Ayonge and Mr C. Fisiy. We are particularly grateful to Dr Pauline O'Neill of the Department of Clinical Microbiology, Louis Jenner Laboratories, St Thomas's Hospital, London SE1, Professor R. G. Huntsman in the Department of Pathology, Lambeth Hospital, London SE1, and Dr S. Welch in the Department of Biochemistry, the London Hospital Medical College, London E1, for performing blood tests on specimens obtained during the study.

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Acquired arterial macroaneurysms of the retina

RICHARD ALAN LEWIS, EDWARD W. D. NORTON, AND J. DONALD M. GASS
From the Bascom Palmer Eye Institute, Department of Ophthalmology,
University of Miami School of Medicine, Miami, Florida

Isolated aneurysms of the four principal divisions of the central retinal artery are found infrequently in older individuals. Robertson (1973) suggested the designation 'macroaneurysm' to distinguish these dilatations of the major arterial branches from the microaneurysms of the retinal capillary-venous plexus. These acquired macroaneurysms are usually unilateral and may be associated with intraretinal oedema, blood, and exudates, subretinal blood and exudation, and rarely, intravitreal haemorrhage which may obscure the aneurysm. Their genesis has been ascribed to hypertension (Robertson, 1973), arteriosclerosis (Robertson, 1973; Ballantyne, 1937), ageing (Shults and Swan, 1974), and various degenerative conditions (Doyne, 1896; Raehlmann, 1902; Ashton and Langley, 1951).

The clinical and fluorescein angiographic findings in 15 cases of acquired arterial macroaneurysms of the retina and our experience with management (Table) are summarized in this report. The findings in an adult woman with an unusual profusion of arterial aneurysms who may represent a variation of this phenomenon are presented separately. Other known causes of aneurysmal dilatation such as Leber's multiple miliary aneurysms (Archer and Krill, 1971) or Coats's syndrome (Egerer, Tasman, and Tomer, 1974), and cavernous haemangioma of the retina (Lewis, Cohen, and Wise, 1975) are excluded from this review.

Case report

CASE I

A 67-year-old white woman stated that, 2 months before her examination at the Bascom Palmer Eye Institute, she had noted an abrupt and persistent diminution of vision in the right eye associated with 'little fine circles of light'. The left eye was amblyopic because of strabismus in childhood. Although she was unaware of a history of hypertension or diabetes mellitus, she had experienced transient ischaemic episodes for many years.

The corrected visual acuity was 20/50 in the right eye and 20/100 in the left, which showed anomalous retinal correspondence. Intraocular pressure was 22 mm Hg in the right eye and 26 mm Hg in the left. Biomicroscopy showed subepithelial nodular and whorl-like opacities in each cornea.

Ophthalmoscopy of the right eye revealed a localized intraretinal haemorrhage along a branch of the inferior temporal artery distal to its fourth bifurcation (Fig. 1*a*). A yellowish-white plug was visible within the artery at that point and appeared to move to and fro synchronously with the carotid pulse. The lumen of the artery proximal to the plug was narrow and markedly irregular. Surrounding the obstruction and haemorrhage was an incomplete ring of circinate deposits. Mild intraretinal oedema extended into the foveal area and there was a delicate hemimacular star temporally. The retina distal to the haemorrhage was otherwise normal. No additional evidence of arterial embolization was found but the calibre of other arteries was irregular, and tapering and deflexion of many arterio-venous crossings were evident. The optic disc had a normal hyperopic configuration and the visual field was normal.

The vessels of the left fundus showed similar hypertensive changes. The left optic disc was irregularly raised suggesting drusen formation, and a sector defect was demonstrated on visual field examination.

Fluorescein angiography demonstrated normal transit of dye to the site of the plug in the right eye but marked delay of filling of the artery distally until the midvenous phase (Fig. 1*b*). No retrograde flow in the artery was demonstrated but late in the study the vessel wall stained intensely at the point of obstruction.

The patient's right brachial artery blood pressure was 180/100 mm Hg. Ophthalmodynamometry was normal and similar in each eye.

Course

The patient was started on antihypertensive medications. Six weeks later the haemorrhage had cleared and an aneurysmal dilatation of the artery was present at the site of the previous obstruction. Ten weeks after initial examination the visual acuity in the right eye had improved to 20/30. Fluorescein angiography showed that the aneurysm was bilobed, that there was no delay in the perfusion of the aneurysm or distal artery, that there was an avascular halo around the aneurysm, and

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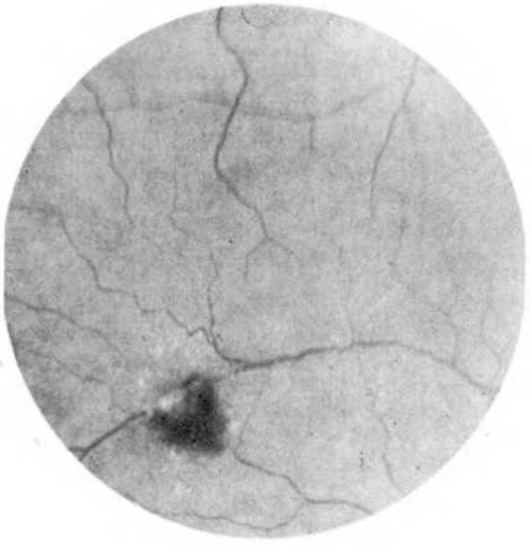
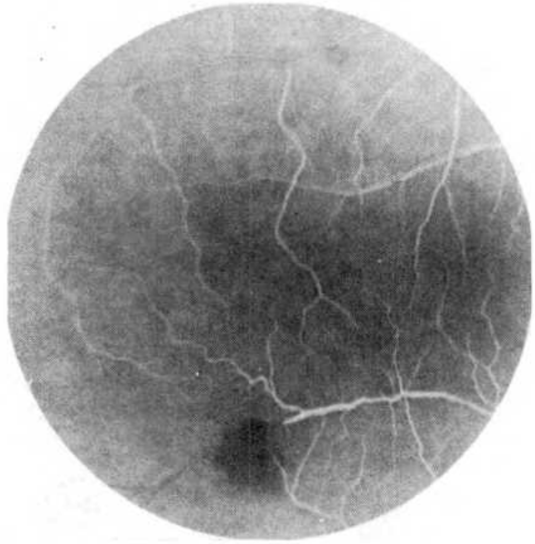
Address for reprints: Richard Alan Lewis, MD, B-2964 Clinical Faculty Office Building, Department of Ophthalmology, University of Michigan Medical Center, 1405 East Ann Street, Ann Arbor, Michigan, 48109, USA



(1a)



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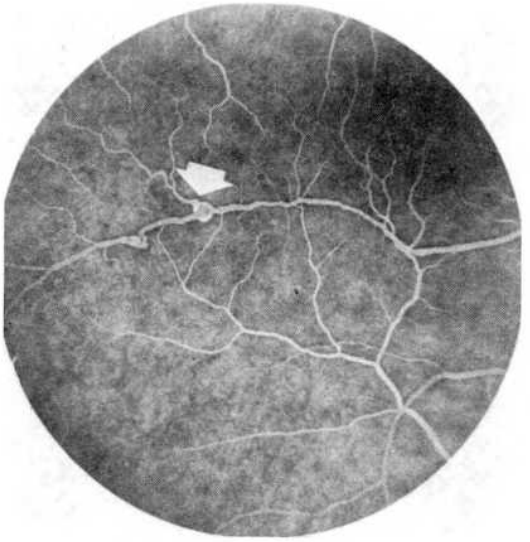


(1d)

FIG. 1

a *Case 1. Haemorrhage partially obscures distal inferior temporal artery of right eye at site of intraluminal plaque*

b *Case 1. Fluorescein angiography on same day shows delayed perfusion beyond intravascular material. Subsequently, antegrade filling of artery ensued but arterial wall stained at site of obstruction*

c *Case 1. Ten weeks later, angiography showed bilobed macroaneurysm at former site of plaque. No delayed perfusion or dye leakage seen. Note irregular calibre of feeding artery*

d *Case 1. More than 4 years later, original aneurysm remains patent and new macroaneurysm at arterial bifurcation has enlarged and formed small satellite (arrow)*

e *Case 1. One year later, aneurysm at bifurcation has enlarged further. Dot haemorrhages scattered near macroaneurysm and another fusiform enlargement of artery appears proximal to arterio-venous crossing (arrow)*

that the adjacent capillaries were slightly dilated (Fig. 1*c*).

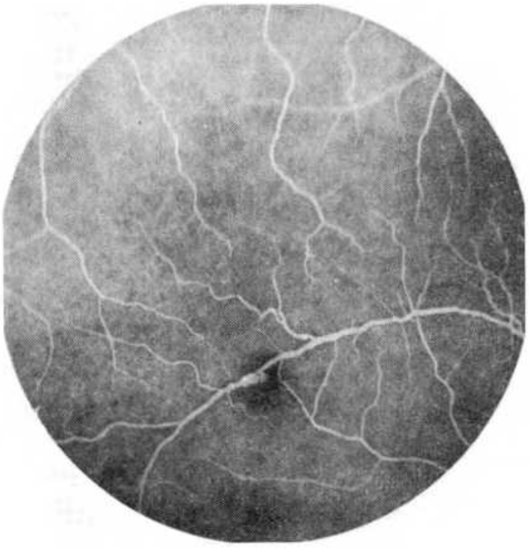
One year after presentation, a new fusiform aneurysm had developed at the next more proximal bifurcation of the artery to the original macroaneurysm, in an area which had not been involved by the plug either ophthalmoscopically or angiographically.

Four years and 3 months after the initial examination the visual acuity in the right eye was 20/50. The original aneurysm was still patent and the aneurysm at the bifurcation had expanded to about five times the width of the vessel and had developed a small satellite along the smaller branch of the bifurcation (Fig. 1*d*).

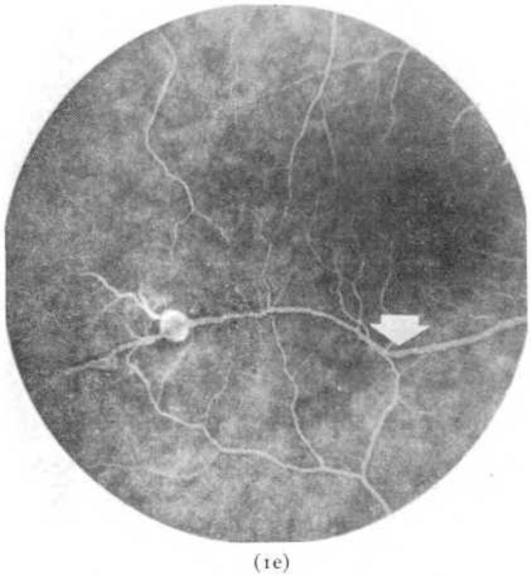
One year later, although the visual acuity was unchanged, there was an increase in intraretinal exudate and oedema surrounding the large aneurysm at the bifurcation. Fluorescein angiography demonstrated delayed flow into the smaller branch of the involved bifurcation, staining of the wall of the larger aneurysm and of the small branch artery, and late leakage into the oedematous retina from each area (Fig. 1*e*). The patient died one month later of a combined cerebrovascular accident and myocardial infarction.

Comment

The evolution and possible aetiology of the arterial macroaneurysms are documented in this hypertensive woman with intracranial vascular symptoms. The process began as an incomplete occlusion of a branch retinal artery; additional aneurysms developed in this damaged



(1c)



(1e)

vessel. The occlusion was attributed to embolic material although the possibility of local vascular disease as a predisposing factor cannot be excluded. The attenuated irregular lumen of the artery proximal to the obstruction and the permeability of its wall to fluorescein suggest damage to the vessel as the obstructing element travelled through it. The absence of visual field defect in the right eye is possibly explained by the incomplete closure of the artery which permitted perfusion of the retina sufficient to prevent ischaemic infarction.

CASE 5

A 49-year-old white woman had sudden blurring of vision in the right eye. Her ophthalmologist observed a haemorrhage overlying an abnormal vessel in the right fundus and an anomalous loop of blood vessels associated with a localized area of exudate in the left eye. The patient was admitted to hospital for extensive investigation, including haematological and serological studies, liver function studies, glucose tolerance test, intravenous pyelography, electrocardiography and skull x rays. The only abnormality was labile systemic hypertension, with a diastolic blood pressure ranging between 90 and 100 mm Hg. The past medical history was unremarkable.

Ocular evaluation

Three months after the onset of symptoms, the visual acuity was 20/40 in the right eye and 20/20 in the left.

Ophthalmoscopy of the right eye identified a macroaneurysm along a small loop in the inferior temporal artery distal to its first bifurcation. The lesion was covered by superficial intraretinal haemorrhage and was surrounded by a broad zone of oedema and a dense ring of exudate which extended into the macula. A bright white plaque was located in the artery just proximal to the aneurysm (Fig. 2*a*). A widened and copper-wire light reflex was evident in most arteries in the fundus and the major arterio-venous crossings showed deflexion and concealment of the venous blood column.

In the left eye a large aneurysm was located at the fourth bifurcation of the superior temporal artery (Fig. 2*b*) and was surrounded by a small zone of retinal oedema and circinate material. A burnished light reflex, irregularities of arterial calibre, and banking and compression of arterio-venous crossings were present throughout the fundus.

Fluorescein angiography of the right eye showed prompt and complete perfusion of the aneurysm and the entire retinal vasculature. The capillary-free zone around the aneurysm was widened and the adjacent microvasculature was moderately altered (Fig. 2*c*). Corresponding to the intraluminal plaque was a defect in the fluorescein column in the artery. The wall of the aneurysm stained with dye and subsequently leaked into the adjacent retina. Angiography of the left eye also demonstrated no evidence of arterial obstruction but some leakage of dye from the walls of the aneurysm.

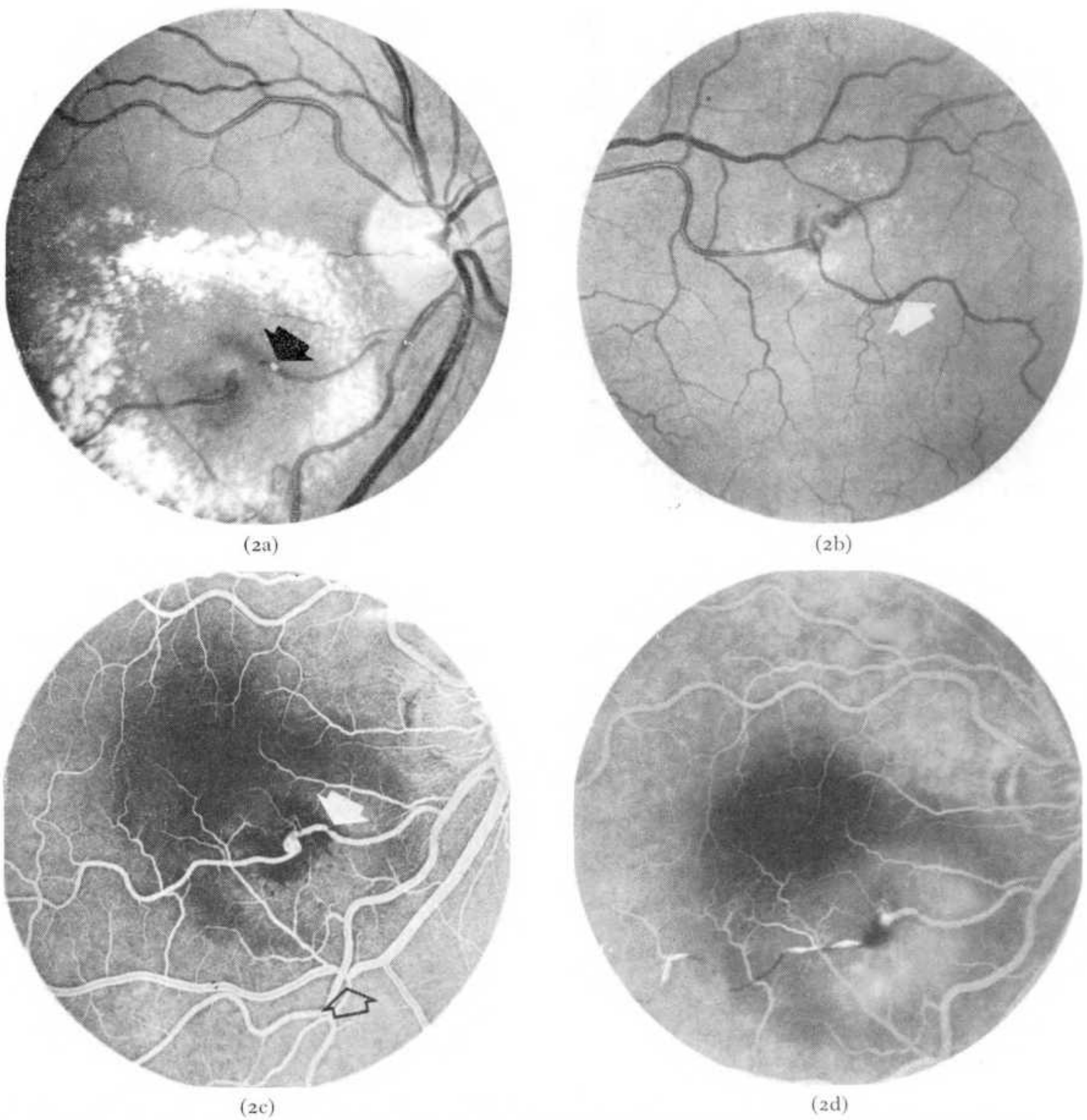
Course

The patient was started on antihypertensive medications. Although the brachial artery blood pressure became normal during the next 2 months (140/76 mm Hg), the visual acuity of the right eye gradually deteriorated to 20/100 with increased circinate material in the macula. The walls of the aneurysm became thickened and grey, and the intra-arterial plaque remained. The arterial segment distal to the aneurysm thinned to about one-third of its original diameter and its blood column was segmented and venous in colour. Fluorescein angiography dramatically displayed obstruction of arterial perfusion and retrograde filling of the distal artery from branch venous channels (Fig. 2*d*). The lesion in the left eye was unchanged. Visual field examination of the right eye showed a superior altitudinal depression within which was a dense scotoma corresponding with

Table *Summary of cases with acquired retinal arterial macroaneurysms*

Case	*Age (yr)*	*Sex*	*Race*	*Eye*	*Visual acuity at onset*	*Treatment**	*Medical history*	*Final visual acuity*
1	67	Female	White	Right	20/50	—	History of transient ischaemic attacks for years Hypertension discovered at onset	20/50 (5 2/12 yr) Died of combined myocardial infarction and stroke
2	64	Female	Black	Right	20/25	—	Severe uncontrolled hypertension for years Goitre, parathyroid adenoma, sarcoidosis	Lost to follow-up Died 4 yr later of stroke
3	58	Male	White	Left	20/25	—	30-year history of hypertension Chemical diabetes for 1 year	20/30 (2 5/12 yr)
4	73	Female	White	Right	CF 1·5 m	A	Poorly controlled hypertension for decades	20/200 (3 yr after treatment)
5	49	Female	White	Right	20/40	A	Hypertension discovered at onset	20/25 (2 2/12 yr after treatment)
				Left	20/15	—		20/15 (no change, 2½ yr)
6	60	Male	White	Right	20/400	X	Normotensive Negative glucose tolerance test	6/200 (3 yr after treatment)
7	69	Female	White	Right	20/300	X	Hypertension for 13 years Angina pectoris for 10 years	20/40 (5 yr after treatment)
8	62	Male	Black	Right	20/300	X	Hypertension discovered at onset	20/30 (2 10/12 yr after treatment)
9	51	Male	White	Right	20/200	A	Diastolic hypertension at onset	20/50 (3 yr after treatment)
10	71	Female	White	Left	20/40	—	Hypertension discovered at onset 3-year history of bilateral vitritis, uveitis, and cystoid macular oedema	20/40 (2 yr)
11	82	Male	White	Left	CF 2·7 m	X	Mild hypertension at onset Adult diabetes mellitus for 25 years	20/100 (lost to follow-up 2/12 yr after treatment)
12	71	Female	White	Right	20/200	X	Hypertension poorly controlled for 12 years	20/30 (1 yr after treatment) Died after abdominal aortic aneurysm
13	59	Female	White	Right	20/200	A	Hypertension Adult diabetes mellitus for 1 year	20/200 (5/12 yr after treatment) Died of combined myocardial infarction and stroke
14	71	Female	White	Right	20/200	—	Hypertension poorly controlled for 13 years Hypercholesterolaemia	20/40 (1½ yr)
15	83	Male	White	Right	20/40	A	Hypertension discovered at onset Spastic paraplegia after septic meningitis as youth	20/25 (4/12 yr after treatment)
16	69	Female	White	Right	20/30	—	Angina pectoris for 10 years	20/40 (1 3/12 year)

*A = Argon photocoagulation X = Xenon photocoagulation — = No treatment



(2a) (2b)

(2c) (2d)

FIG. 2 a *Case 5. Macroaneurysm of inferior temporal artery of right eye surrounded by macular oedema and dense circinate ring. Bright white plaque located in artery proximal to macroaneurysm (arrow)*

b *Case 5. Horse-shoe shaped macroaneurysm of superior temporal artery of left eye is associated with small zone of retinal oedema and exudates. Note small fusiform enlargement of adjacent branch artery (arrow)*

c *Case 5. Midvenous phase of fluorescein angiogram of right eye. Note defect in fluorescein column corresponding to bright plaque in Fig. 2a (white arrow). Disruption of laminar venous flow is present at arterio-venous crossing (open arrow)*

d *Case 5. Two months later, late venous angiogram shows obstruction of arterial perfusion at macroaneurysm and segmental retrograde filling of distal artery from venous tree. Macular oedema is more extensive*

the aneurysm, and in the left eye a relative scotoma corresponding with that aneurysm. Because of the failing central vision in the right eye, 68 applications (100 μm spot size, 0·1 s duration, 150—300 mW) of argon laser photocoagulation were applied to the aneurysm and to the area surrounding it. Seven weeks after treatment the visual acuity was 20/25 in the right eye, the aneurysm had disappeared, and oedema and fatty deposits had begun to resorb, but 26 months after photocoagulation the visual acuity was unchanged. Nearly all the circinate material in the right fundus had cleared, leaving a patchy area of depigmentation in the macula. Hypopigmented scars and grey sheathing of the attenuated artery indicated the site of therapy. Apart from minor changes in the pattern of the circinate ring, the aneurysm of the left eye was unaltered.

Comment

The retinal vasculature in both eyes of this woman showed evidence of long-standing systemic hypertension. Proximal to the arterial macroaneurysms in the right eye was an intraluminal plaque. Although no additional fragment or embolus was seen at the site of the vascular anomaly, the aneurysm was well established at the time of our examination. Whether the existing plaque or factors within the aneurysm or the arterial wall precipitated the arterial occlusion is a matter for conjecture. Photocoagulation promptly eliminated the aneurysm as the source of intraretinal oedema and central visual acuity improved. The macroaneurysm in the left eye was followed for 2½ years with no important changes or effects upon vision.

CASE 9

A 51-year-old white man had a corrected visual acuity of 20/20 in each eye several months before he experienced the abrupt onset of a grey central scotoma in the right eye. About 3 weeks later, the visual acuity was 20/200 in the right eye and 20/20 in the left.

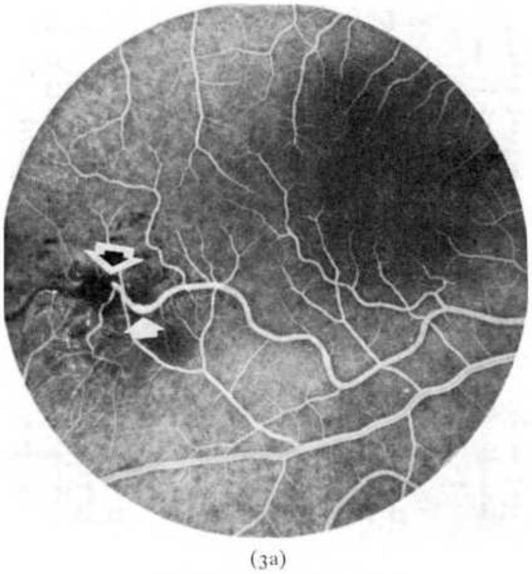
Temporal to the macula of the right eye a macroaneurysm was situated at the fifth bifurcation of the inferior temporal artery. Distal to the aneurysm, the blood in the branch artery appeared desaturated. The aneurysm was surrounded by a broad zone of thickened oedematous retina extending into the fovea and there were patches of yellow exudates in an incomplete ring pattern temporal and inferior to the aneurysm. The retinal arterial tree demonstrated an increased light reflex, moderate arterial tortuosity, irregular calibre, and arterio-venous compression. In the periphery at the 9 and 12 o'clock meridians were numerous sheathed vessels and intraretinal vascular changes suggestive of old branch retinal vein occlusions.

The vessels of the left fundus were normal except for a copper-wire arterial light reflex and mild arteriovenous crossing defects.

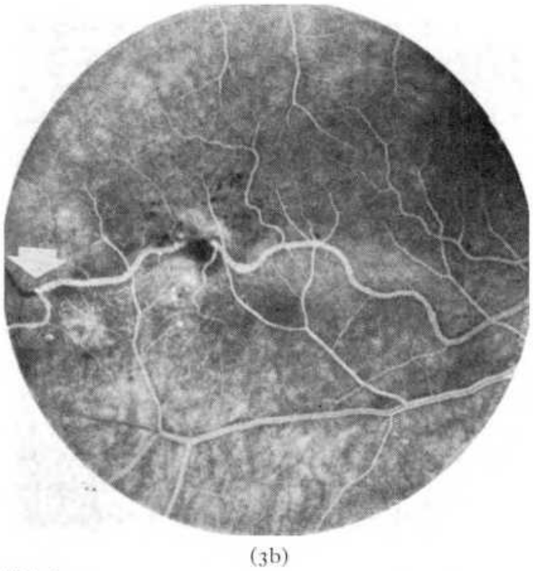
Fluorescein angiography revealed two slight fusiform enlargements of the feeding artery and delay of flow at the site of the macroaneurysm (Fig. 3*a*). Although the dye eventually perfused the arterial segment distal to the aneurysm, it halted again at the next major bifurcation (Fig. 3*b*). Both the aneurysm and the considerable local intraretinal angiopathy leaked dye in the later phases of angiography.

Course

The patient's brachial artery blood pressure was 150/95 mm Hg. Ophthalmodynamometry was normal and the same in each eye. Altogether 58 applications of argon laser photocoagulation (100 μm spot, 0·2 s duration, 300 mW) were directed at the aneurysm and to local zones of microangiopathy. Two months later the visual acuity in the right eye was 20/50, the aneurysm was obliterated, and the retinal oedema and exudate were much reduced. Angiography showed that the artery distal to the aneurysm was totally occluded. Ten months



(3a)



(3b)

FIG. 3

a *Case 9. Fluorescein angiography at midvenous phase showed two fusiform enlargements of feeding artery (white arrow) and impediment of flow at macroaneurysm (striped arrow)*

b *Case 9. Later in venous phase, an additional segment of artery perfuses, but flow halts at next bifurcation (arrow). Note microangiopathy in adjacent vascular bed* after photocoagulation, however, an arterial-arterial collateral diverted flow around the site of the occluded aneurysmal segment into the distal arterial segment. Three years after therapy the visual acuity was 20/50 and no new lesions had appeared.

Comment

Although this patient had only borderline diastolic hypertension, there was evidence of hypertensive retinal vascular changes. Fluorescein angiography showed arterial occlusions although no intraluminal emboli were seen clinically. Photocoagulation quickly eliminated the source of macular oedema and improved visual acuity.

CASE 16

A 69-year-old white woman experienced 'flashing lights' and triangular floaters in her right eye for 2 months before she consulted her ophthalmologist. She stated that the visual acuity in the right eye had never been as clear as that in the left. Although she had had angina pectoris for about 10 years, she had no history of hypertension or medical problems other than bilateral mastectomies for fibrocystic disease.

The visual acuity was 20/25 in the right eye (−0·75 D sph., +3·25 D cyl., axis 120°) and 20/20 in the left eye (+1·75 D sph.). Ophthalmoscopy of the right fundus showed numerous arterial macroaneurysms involving only the temporal retinal vasculature (Figs 4*a*, *b*). These varied from small fusiform enlargements of the arterial wall to irregular saccular swellings four or five times the diameter of the feeding vessel. None of the lesions was haemorrhagic although several large ones were surrounded by small zones of oedematous retina demonstrated by circinate deposits. One branch of the superior temporal artery with pipestem sheathing and irregular attenuation of its lumen became a ghost vessel more distally, and a resolving cotton-wool patch was noted in its distribution. No delay of perfusion was identified through any of the aneurysms during fluorescein angiography. A cluster of tortuous collateral vessels rimmed one of the larger aneurysms (Fig. 4*c*). The left fundus was normal.

The brachial artery blood pressure and the results of ophthalmodynamometry were normal and symmetrical.

Fifteen months later, the corrected visual acuity was 20/40 in the right eye. Central metamorphopsia and a paracentral scotoma were demonstrable in the right eye on an Amsler grid. At least 18 arterial aneurysms were visible on various branches of the temporal vasculature. No abnormalities of the nasal vessels were seen. Several of the aneurysms were well anterior to the equator and surrounded by circinate rings. Several aneurysms in the posterior pole were overlaid with recent haemorrhages. Some of the previously recognized aneurysms had enlarged considerably and others appeared in formerly normal areas (Fig. 4*d*). Mild cystoid macular oedema was noted. Fluorescein angiography dramatically showed the vascular malformations and mild leakage from multiple macroaneurysms. The left eye was normal. No treatment was instituted.

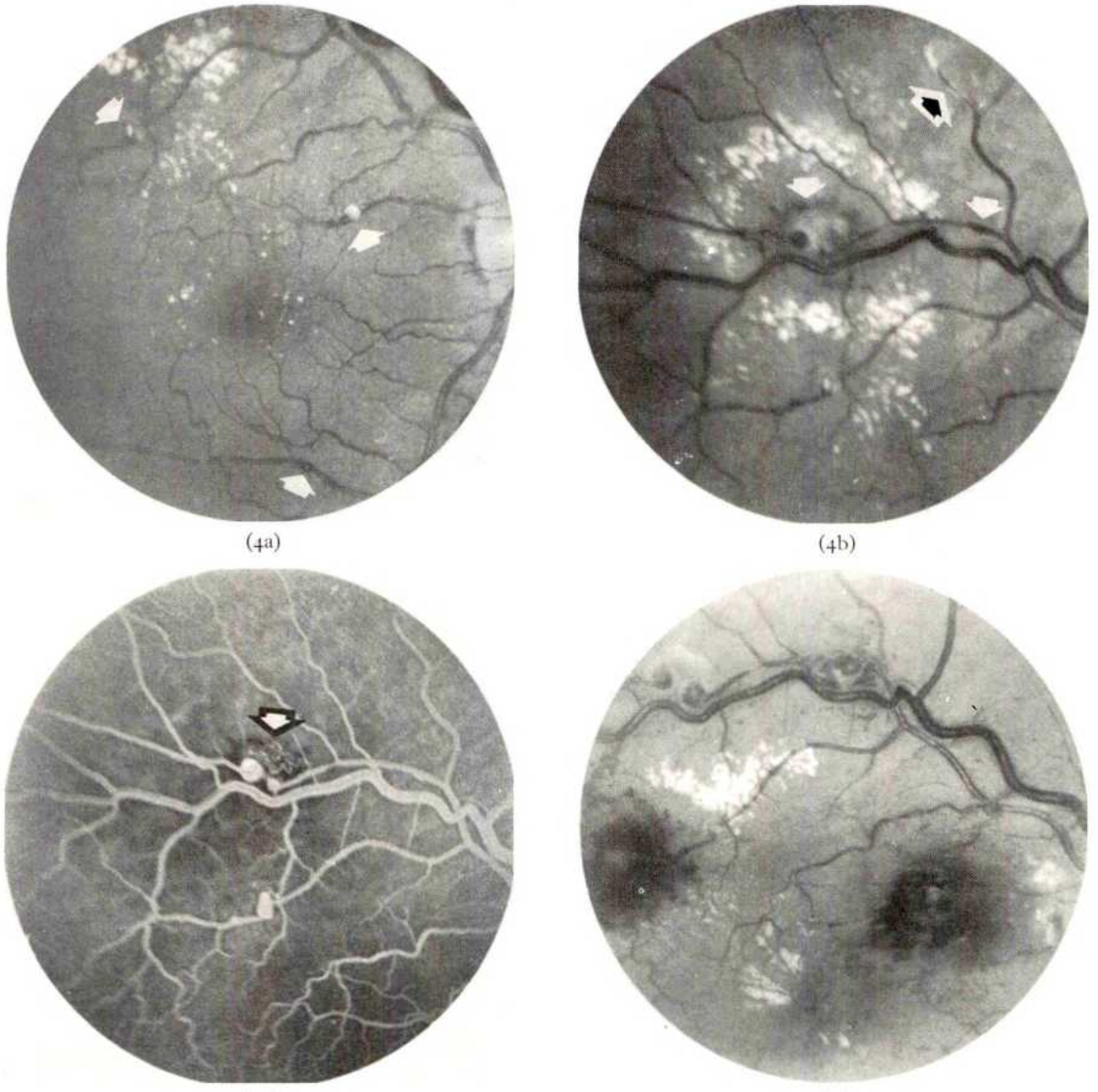
Comment

This normotensive woman presents an exceptional number and distribution of arterial aneurysms without vascular anomalies. The condition does not resemble the syndrome of Leber's multiple miliary aneurysms and it may be incorrect to group this patient with the cases of acquired retinal arterial macroaneurysms described above. The findings are not therefore included in this summary. It is not known whether the lesions were solely acquired or influenced by unseen or congenital factors.

Discussion

Although aneurysms of the major arteries have been recognized in various retinal disorders for many decades (Doyne, 1896; Story and Benson, 1883), the designation 'macroaneurysm' was applied recently to a specific acquired lesion by Robertson (1973) in his review of 13 cases. Six other cases have been reported more recently (Hudomel and Imre, 1973; Shults and Swan, 1974). The average age at presentation of our patients was 66 years (median 67; range 49 to 83). Nine of our 15 patients were female, which confirms the reported prevalence of this condition in females. The relationship of this finding with the recognized predominance of intracranial aneurysms in women after the age of 50 years (Walsh and Hoyt, 1969) is obscure.

Thirteen of our patients either had a history of systemic hypertension or hypertension was discovered at the time of consultation. Three of the 13 also had diabetes mellitus of adult onset although none had clinically significant diabetic retinopathy. The association of severe hypertension with retinal arterial aneurysms appears to have been first reported by Fernandez (1920) in a 54-year-old man who died 40 days after presentation of a cerebral haemorrhage. Robertson (1973) emphasized the coexistence of hypertension with the retinal pathology. More than half of his patients had mild to severe hypertension. He also suggested that the occurrence of macroaneurysms was not necessarily an ominous prognostic sign, since two of his patients survived more than a decade after discovery of the lesion. However, four of our patients died between 9 months and 5¼ years after presentation, one of a stroke, two of combined myocardial infarction and stroke, and one shortly after resection of a symptomatic abdominal aortic aneurysm. While a retinal arterial macroaneurysm *per se* may not be prognostic of early death, it may herald the discovery of coexisting hypertension or other systemic vascular disease which could affect a patient's life expectancy. At a minimum, therefore, we recommend measurement of the systemic blood pressure during the investigation of patients with this lesion. Ophthalmodynamometry, on the other



(4a) (4b)

(4c) (4d)

FIG. 4 a *Case* 16. *Several macroaneurysms (arrows) of temporal arteries of right eye with associated exudates*
b *Case* 16. *Other macroaneurysms superotemporally (white arrows). One branch artery is sheathed and partially occluded (arrow)*
c *Case* 16. *Angiography shows cluster of small tortuous collateral vessels around one of the macroaneurysms (arrow)*
d *Case* 16. *Fifteen months later, several macroaneurysms have enlarged and some are obscured by blood (compare with Fig.* 4a *and* b)

hand, was not revealing in the patients tested.

One patient (Case 5) had bilateral aneurysms. Among patients affected unilaterally, 11 (79 per cent) had the right eye involved. We cannot explain this prevalence, although it follows the trend in other series (Robertson, 1973; Shults and Swan, 1974). All aneurysms were temporal to the optic disc and in 10 of 16 affected eyes, the lesions were superior to the horizontal raphe, including one patient (Case 6) with two aneurysms on a cilioretinal artery. Macular oedema and circinate retinopathy were no more frequent with superior than with inferior malformations.

Of 17 separate aneurysms in these 16 eyes, seven

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occurred at an arterial bifurcation and three more at a point of arterio-venous crossing, and in each of these there were intraluminal plaques in the same or adjacent branch arteries (Cases 3, 7, 14). Among the other seven aneurysms, four were accompanied by clinical or angiographic evidence of complete or incomplete arterial occlusion and another by a resolved branch retinal vein occlusion elsewhere in the same fundus. Two patients (Cases 5, 8) had arcuate altitudinal field defects at presentation, suggesting a previous major arterial occlusion at the optic disc.

Various factors have been implicated in the production of arterial aneurysms. Doyne (1896) attributed his findings to a 'plugged beaded vessel'. Robertson (1973) considered ageing, hypertension, and generalized arteriosclerosis to be important considerations. Interestingly, one of his patients was described as having multiple cholesterol emboli proximal and distal to the aneurysm, and another had a branch arterial occlusion.

Our observations on Case 1 suggest that arterial aneurysms may develop as a result of focal damage to the vascular wall. The patient presented with a bright intraluminal plaque and angiographic evidence of an incomplete arterial occlusion. The plaque was probably embolic in origin, although thrombosis from local vessel disease cannot be excluded. Subsequently she developed aneurysms both at the site of the plaque, at the next proximal bifurcation of the artery, and along its dichotomous branch in which an intraluminal plaque had also been seen. We believe that an injury to the vessel wall could allow loss of its functional continuity and lead to the formation of an aneurysm. The fact that most aneurysms form at arterial bifurcations or at arterio-venous crossings may imply either more common sites of embolic impact or zones of intrinsic vascular weakness. Similarly, the observation of intra-arterial plaques in six of 16 affected eyes and the history and objective findings of vascular occlusions in nine patients further suggests a setting for vessel damage. One can speculate about the role of hypertension in predisposing or fomenting aneurysms after such internal injury. Certainly the high incidence of documented systemic hypertension and hypertensive vascular changes in both affected and fellow eyes cannot be ignored.

With the enhancement of fluorescein angiography, intraretinal microvascular abnormalities in the vicinity of aneurysm were recorded in about one-half of the aneurysms. These alterations included local widening of the periarterial or peri-aneurysmal capillary-free zone, dilatation of the adjacent capillary bed with small zones of capillary non-perfusion, capillary microaneurysms rimming the avascular zone around the aneurysm, and fine intra-arterial collateral formation. In several patients we observed the evolution of these microvascular changes. Robertson comments on 'abnormal dilatation or neovascularization within the area of serous fluid surrounding the macroaneurysm' in two of his patients, in one of whom the anomaly was apparently present before the development of the aneurysm. He speculated that chronic venous obstruction might influence their origin. Alternatively, these microvascular changes resemble the reorganization of small vessel networks which have been shown in experimental embolic arterial occlusions by Dollery, Henkind, Paterson, Ramalho, and Hill (1966), Henkind (1966), and Klein, Klein, Henkind, and Bellhorn (1971). It is conceivable that our observations represent a similar compensation of local blood flow, caused by either previous embolic matter or mechanical forces in the damaged or expanding arterial wall.

The visual complication of acquired retinal artery aneurysms most commonly responsible for the patients' complaints is macular oedema with circinate retinopathy. Two patients in our series presented with vitreous haemorrhage. Local intraretinal haemorrhage at the site of the aneurysm was noted in one-half of the affected eyes during the period of observation but implied no predictive value of visual function or course. In all cases of macular oedema and other aneurysms with local oedema and fatty exudate, fluorescein angiography demonstrated staining of the aneurysmal wall, suggesting defective integrity of the endothelium permitting dye leakage into the surrounding retina. Fluorescein also leaked from zones of microvascular abnormalities.

Among the 16 eyes comprising this survey, five eyes were followed without therapy, and one patient was lost to ophthalmic observation after discovery of her lesion (Case 2). Three of the five patients observed without therapy had good and stable visual acuity in the affected eye for up to 5 years after presentation. One patient spontaneously improved from 20/400 to 20/30 acuity in the 3 months before consultation and remained at that level for 16 months. The fifth patient had chronic bilateral uveitis, vitritis, and cystoid macular oedema, and 20/50 vision in each eye. Because the macroaneurysm did not appear to contribute significantly to the macular oedema, photocoagulation was not considered. Six months later the visual acuity was unchanged in each eye. All untreated aneurysms remained patent during the follow-up period.

Five eyes were treated with xenon arc photocoagulation. Although most of these patients were followed-up from 6 weeks to 7 months before treatment, the level of visual recovery was judged to be unsatisfactory. Treatment resulted in visual improvement of two or more lines of a Snellen chart in three of five eyes. One patient (Case 11) who had presented with vitreous haemorrhage and had evidence of an epiretinal membrane with macular traction from the aneurysm before treatment, was lost to follow-up 7 weeks after therapy with an unchanged visual acuity of 20/100. Another patient (Case 6) presented with a dense senile cataract and developed a cellophane membrane in the macula after treatment.

Of five eyes treated with argon laser photocoagution, three showed improvement of two lines or more of Snellen acuity. One other patient developed a branch arterial occlusion distal to the area of treatment and pretreatment visual acuity of 20/200 was unchanged nearly 3 years later. The other patient had a history of paracentral chorio-retinitis and retinal vascular occlusions. The visual acuity remained unchanged at 20/200 5 months after treatment.

All treated aneurysms were obliterated both ophthalmoscopically and angiographically. Visual improvement was documented as early as 3 days and on average 6 to 8 weeks after photocoagulation. Our experience suggests that photocoagulation may speed visual improvement in patients with macular oedema and circinate retinopathy who have not improved spontaneously after 3 months of observation. Photocoagulation is probably indicated if the aneurysm increases in size and if further exudation results in failing visual acuity (Gass, 1972). However, additional experience with photocoagulation is required to confirm these impressions. Macroaneurysms not affecting macular function probably do not need photocoagulation.

Summary

Fifteen patients with acquired arterial macroaneurysms of the retina, and an additional woman patient with some 18 aneurysms of the temporal retinal arterial tree of one eye, are described. Acquired aneurysms occur in patients in their sixth decade and older, are usually unilateral, and occur on the major arterial branches posterior to the equator. Customarily only one or two aneurysms are present. Most patients have a history of poorly controlled systemic hypertension or a raised blood pressure at the time of discovery of the macroaneurysm. Focal embolic damage to arterial walls should be considered in the investigation of these patients. In patients with decreased vision from macular oedema and circinate retinopathy, photocoagulation of the macroaneurysm may hasten the improvement in visual acuity.

We thank Victor T. Curtin, MD, and James C. Major, MD, for permission to report the findings in their patients. We also thank William L. Hutton, MD, who generated our initial interest in this subject.

Three of these cases were presented in part at the International Fluorescein Conference, Tokyo, Japan, on 1–6 February 1972.

The medical history of Case 2 was previously reported in part by Burr, Farrell, and Hills (1959).

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Angioid streaks and sickle haemoglobinopathies

K. C. NAGPAL, G. ASDOURIAN, M. GOLDBAUM, D. APPLE, AND M. F. GOLDBERG
From the Sickle Cell Eye Clinic of the University of Illinois Eye and Ear Infirmary, Chicago, Illinois

Doyne (1889) described the clinical picture of angioid streaks. Groenblad (1929) reported the association of skin disease with angioid streaks. Strandberg (1929) carried out histopathological examinations of skin biopsies from Groenblad's patients and proved the abnormality to be that of pseudoxanthoma elasticum. Subsequently, angioid streaks have been reported in association with several other diseases, such as Paget's disease (Paton, 1972), acromegaly (Holloway, 1927; Howard, 1963; Paton, 1963), and Ehlers-Danlos syndrome (Green, Friedman-Kien, and Banfield, 1966).

The association of angioid streaks with sickle cell disease was first reported by Geeraets and Guerry (1960a) who described an incidence of angioid streaks of 6 per cent in a selected population of sickle cell patients (five of 69 cases). Subsequent reports have not substantiated such a high incidence of angioid streaks concomitant with sickle cell disease (Welch and Goldberg, 1966; Paton, 1972). Geeraets and Guerry (1960b) also reported elastic tissue degeneration in sickle cell patients and speculated whether intraocular and general elastic tissue degeneration in sickle cell disease represented a coincidental or true causative relationship. Skin biopsy studies in two sickle cell patients (Paton, 1972) failed to show any abnormality of elastic tissue.

Since we had an opportunity to examine a large series of sickle cell patients, the purpose of this communication is to report the incidence of angioid streaks in various sickle haemoglobinopathies. It is also our intention to demonstrate that no other disease, such as pseudoxanthoma elasticum, Paget's disease, or acromegaly, was associated with angioid streaks in our sickle cell patients. Because others have found elastic tissue alterations in sickle cell patients, we examined the skin of all our patients, specifically looking for elastic tissue changes histopathologically.

We also investigated the relationship between the severity of sickle cell retinopathy and the presence of angioid streaks.

Clinical data and methods

A total of 356 patients had been screened in the Sickle Cell Eye Clinic of the University of Illinois by May 1975. The haemoglobin electrophoresis of these patients showed that 162 had sickle cell anaemia (Hb SS); 101 sickle cell-haemoglobin C disease (Hb SC); 49 sickle cell trait (Hb AS); 34 haemoglobin S-thalassaemia (Hb S-thal); eight haemoglobin AC; and two haemoglobin CC.

Of these 356 patients five had angioid streaks and were investigated in detail. Investigations included detailed physical examination and the following laboratory determinations: Hb levels, Hb electrophoresis, serum calcium (normal 5·0 ± 0·5 mEq/litre and phosphate (normal 1·5–2·9 mEq/litre) levels, alkaline phosphatase (normal 20–124 international units/ml), skull and pelvic *x*-ray films, and skin biopsy. Haematoxylin and eosin stain, Verhoeff–van Gieson stain for elastic tissue, and von Kossa stain for calcium deposition were done in all cases to rule out elastic tissue abnormalities.

Ocular examination included visual acuity determination in both eyes and anterior segment examination with the slit lamp. A detailed fundus drawing with the binocular indirect ophthalmoscope, fundus photography, and fluorescein angiography were carried out in all cases.

Case reports

Case 1, a 42-year-old black woman with Hb SS, was first seen in November 1972. Her history included several episodes of sickle cell crises with episodic fever, joint pain, abdominal pain, and jaundice. She also had a history of mild systemic hypertension. Her blood pressure on systemic examination was 195/95 mm Hg.

Visual acuity was 20/30 in both eyes. Slit-lamp examination revealed positive conjunctival sickling sign. The right fundus showed small angioid streaks localized in the peripapillary region and two black sunbursts (chorio-retinal scars) at 12 and 2 o'clock in the retinal periphery. The macula was not involved.

The left eye also showed peripapillary angioid streaks without involvement of the macula. An area of neovascularization at 1.30 o'clock in the equatorial region leaked dye on fluorescein angiography; argon laser photocoagulation successfully occluded the feeder vessels.

Follow-up in August 1974 showed no change in angioid streaks or sickle retinopathy. Laboratory evaluation showed Hb level 9·6 g/100 ml; Hb SS by electrophoresis; serum calcium 4·8 mEq/litre; phosphate

Address for reprints: Morton F. Goldberg, MD, University of Illinois, Eye and Ear Infirmary, 1855 W. Taylor Street, Chicago, Illinois 60612, USA

2·6 mEq/litre; alkaline phosphatase 67 units/ml. Skull and pelvic *x*-ray films were normal. Skin biopsy showed no evidence of subepithelial or dermal elastic tissue alterations.

Case 2, a 46-year-old black man with Hb SC, was first seen in October 1971 with the diagnosis of vitreous haemorrhage in both eyes. His past history was unremarkable. Systemic examination was normal.

Visual acuity was 20/50-2 in the right eye and 20/25 in the left. Fundus examination revealed angioid streaks near the disc and a large patch of neovascularization in the right eye at 10 o'clock with a small vitreous haemorrhage in the temporal equatorial zone. The left eye showed sea-fans at 9.30, 12, 1, and 3 o'clock and angioid streaks around the disc.

Follow-up in September 1974 showed small angioid streaks in both eyes, which were confined to the peripapillary area; the maculae were not involved.

Laboratory findings were as follows: Hb 10·2 g/100 ml; Hb SC by electrophoresis; serum calcium 4·9 mEq/litre; phosphate 2·1 mEq/litre; alkaline phosphatase 34 units/ml. Skull and pelvic *x*-ray films showed findings consistent with sickle cell anaemia. Skin biopsy was normal.

Case 3, a 36-year-old black man with Hb SS, was seen in July 1974 for sickle cell retinopathy. The patient had had a few sickle cell crises, urinary tract infection, renal vein thrombosis, and upper respiratory tract infection. General physical examination was normal.

Visual acuity was 20/20 in both eyes. Slit-lamp examination showed positive conjunctival sickling sign. Fundus examination revealed prominent angioid streaks in both eyes (Figs 1 and 2) radiating from the peripapillary region. The maculae were not involved. The retinal periphery showed arteriolar occlusions typical of sickle cell disease. No neovascularization was seen.

Laboratory findings were as follows: Hb 10·9 g/100 ml; Hb SS by electrophoresis; serum calcium 4·9 mEq/litre; phosphate 2·4 mEq/litre; alkaline phosphatase 40 units/ml. Skull and pelvic *x*-ray films were normal; abdominal *x*-ray films revealed gallstones. Skin biopsy showed no elastic tissue degeneration.

Case 4, a 47-year-old black man with known Hb S-thal, was first seen in May 1970 with the complaint of poor vision in the right eye. He had had several episodes of sickle cell crises for which he had received symptomatic treatment.

Ocular examination showed visual acuity of perception of light in the right eye and 20/20 in the left. Slit-lamp examination was unremarkable. Vitreous haemorrhage prevented fundus examination of the right eye. The left eye showed prominent wide angioid streaks radiating from the peripapillary region; the macula was not involved.

Patches of neovascularization at 1 and 3 to 4 o'clock in the equatorial region of the left eye were photocoagulated in 1971.

A cataract was removed from the right eye in September 1974. The retina showed extensive degeneration with retinal pigmentary changes and vascular occlusions in both the central and the peripheral area. The inferior retina not involving the macula was detached with vitreous traction and breaks in this area. White fibrous tissue was seen at 8 o'clock. There was no improvement in vision after cataract extraction.

Laboratory findings were as follows: Hb 9·6 g/100 ml; Hb S-thal by electrophoresis; serum calcium 5·1 mEq/litre; phosphate 2·1 mEq/litre; alkaline phosphatase 26 units/ml. Skull and pelvic *x*-ray films suggested Paget's disease or metastatic carcinoma. Alkaline phosphatase levels were normal repeatedly. Systemic examination showed no evidence of malignancy. Skin

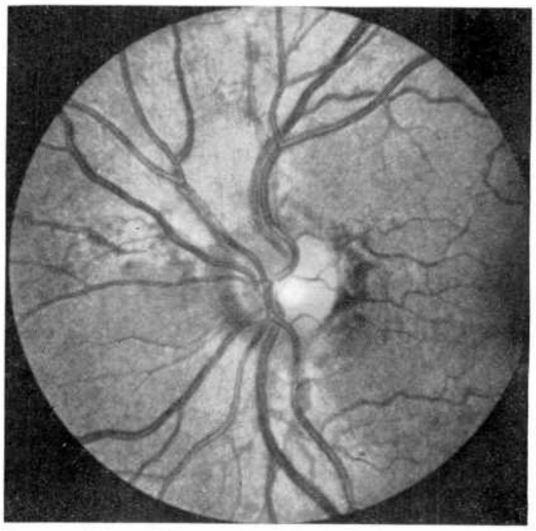

FIG. 1 *Case 3, left eye. Fundus photograph showing angioid streaks*

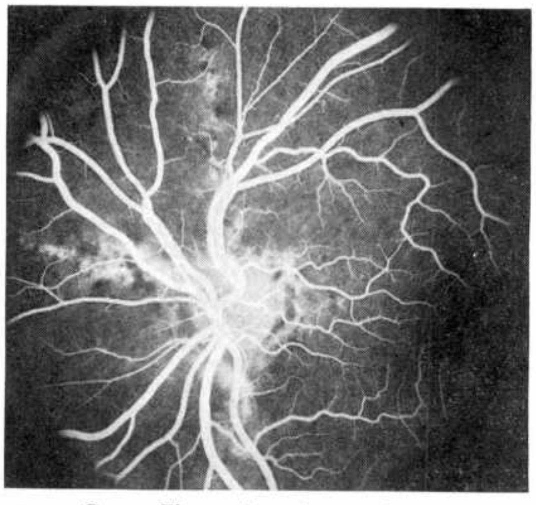

FIG. 2 *Case 3. Fluorescein angiogram of same eye as in Fig. 1, showing hyperfluorescence of angioid streaks*

biopsy was normal; no elastic tissue degeneration was found.

Case 5, a 49-year-old black man with Hb SS, was first seen in January 1973. History showed that he had had several episodes of sickle cell crises and joint pain which had been treated symptomatically.

Visual acuity of 20/30 in both eyes improved to 20/20 with -0·5D sph. in both eyes. Slit-lamp examination showed positive conjunctival sickling sign. In both eyes fundus examination revealed asteroid hyalitis and small angioid streaks, particularly in the peripapillary region. The macular area was not involved with streaks, although there were multiple drusen of both maculae. The retinal periphery showed occluded retinal arterioles in both eyes, but no neovascularization.

Follow-up in September 1974 showed no change in ocular status. Laboratory determinations showed Hb 10·5 g/100 ml; Hb SS by electrophoresis; serum calcium 4·6 mEq/litre; phosphate 2·3 mEq/litre; alkaline phosphatase 33 units/ml. Findings on skull and pelvic *x*-ray films were consistent with sickle cell anaemia. Skin biopsy demonstrated no evidence of elastic tissue degeneration.

Discussion

Although the association of sickle cell haemoglobinopathies with angioid streaks is well documented, the reported incidence has varied from 0·95 to 6 per cent (Geeraets and Guerry, 1960a; Welch and Goldberg, 1966; Paton, 1972). These groups comprised a small number of patients. Since we examined a large number of patients, the occurrence of five cases in 356 patients (1·4 per cent) may represent the truer incidence of angioid streaks in sickle cell haemoglobinopathies. These data are close to the incidence reported by Paton (1972) who documented 1·33 per cent incidence of angioid streaks in various sickle haemoglobinopathies. The series described by Geeraets and Guerry (1960a) gave a very high incidence of angioid streaks in relation to sickle cell disease, perhaps because of their selection of patients. The incidence of angioid streaks in our series may not be entirely accurate either, because of a certain degree of patient selection.

Detailed investigations of our patients failed to show evidence of other diseases known to be associated with angioid streaks except in one case: the radiologist suspected Paget's disease or metastasis from a systemic malignancy in Case 4, but repeated serum alkaline phosphatase determinations and systemic examination were normal. Skin biopsy specimens, which were examined by an ophthalmic pathologist, a dermatologist, and a pathologist, revealed no evidence of elastic tissue degeneration. Moreover, we are not able to support the finding by Geeraets and Guerry (1960b) of widespread elastic tissue degeneration in sickle cell disease, which might have been causally related to cracks in Bruch's membrane. Our findings lend support to the contention of Paton (1972) that it is highly unlikely that an elastic tissue defect exists in addition to Hb abnormality. We are unable to confirm Paton's hypothesis that chronic haemolysis results in deposition of iron in Bruch's membrane, thereby rendering it more brittle and prone to crack; however, this appears to be a more convincing argument than that involving elastic tissue degeneration.

The presence of angioid streaks could not be related to the severity of retinopathy. Two patients with sickle cell anaemia and angioid streaks had very mild retinopathy, whereas two patients with Hb S-thal and one with Hb SC had peripheral retinal neovascularization and severe retinopathy. These observations on the severity of the proliferative retinopathy agree with previous reports that retinal neovascularization is characteristic of certain varieties of sickle cell disease, particularly Hb SC and Hb S-thal (Welch and Goldberg, 1966; Goldberg, 1971a, b; Goldberg, Charache, and Acacio, 1971). Our observations also support the earlier hypothesis (Goldberg, 1975) that visual disability from the streaks is uncommon in patients with haemoglobinopathy. None of our patients had haemorrhagic macular involvement by the streaks.

An interesting observation that we are unable to explain is the age of patients reported by Geeraets and Guerry (1960a), by us, and by Paton (1972). All those described by Geeraets and Guerry (1960a) were younger than 30 years, whereas those reported by Paton (1972) and all those with angioid streaks in our series were over 30 years old. In our series of patients there was a large number of paediatric patients, yet we did not see a single case of angioid streaks in that group.

Summary

Five patients had angioid streaks associated with sickle cell haemoglobinopathy. Other diseases associated with angioid streaks were ruled out, as was elastic tissue degeneration in sickle cell patients. After studying over 350 patients, we believe the incidence of angioid streaks in sickle cell disease to be between 1 and 2 per cent.

We thank Dr Ronald Welsh, Professor of Pathology, Louisiana State University, and the University of Illinois Department of Dermatology. We acknowledge our appreciation to Jane Lantz for editing the manuscript, and to Wilma Jones and Barbara Dombkowski for secretarial assistance. We also express our thanks to Bruce Busse for photography. This work was supported in part by contract 72-2956B and grant IP 15168 from the National Heart and Lung Institute, Bethesda, Maryland, USA.

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Reticular tapeto-retinal dystrophy
As a possible late stage of Sjögren's reticular dystrophy

GERALD A. FISHMAN, MICHAEL B. WOOLF, MORTON F. GOLDBERG,
AND BRUCE BUSSE
*From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary,
Chicago, Illinois*

Two patients with a reticular dystrophy of the retina were noted to have fundus changes reminiscent of those reported in patients with Sjögren's reticular dystrophy. Our subjects were older than previously reported cases of Sjögren's dystrophy and manifested more extensive retinal abnormalities involving both the retinal pigment epithelium and photoreceptors. Similarities were noted both ophthalmoscopically and on fluorescein angiography. Reduced central visual acuity, abnormal findings on electroretinography, ophthalmoscopically evident hypopigmentation, and probable atrophy of the retinal pigment epithelium were specific to the more advanced condition.

Case reports

Case 1, a 72-year-old white man, had a 6-year history of bilateral decrease in central vision and a slowly progressive loss of night vision over the past 10 years. The patient could not recall having been examined by an ophthalmologist before the onset of these symptoms. His father allegedly had had similar difficulties with both central and night vision which had begun when he was in his forties, although further details of his eye disease were not available. Other family members, including seven children, were said to be not as yet affected. The patient was unaware of either Swedish or Dutch ancestors.

When he was seen in September 1974, the patient's best corrected vision was 3/200 in the right eye and 10/200 in the left, with correction +1D sph. in the right eye and +1·25D sph. in the left. His general health was good. External and motility examinations were normal, both pupils reacted normally to direct and consensual light stimuli, slit-lamp examination of the anterior segments was normal, as was the intraocular pressure of 14 mm Hg in the right eye and 12 in the left. There was no increase in cellularity of the vitreous. The patient had 1 to 2+ bilateral nuclear sclerotic and anterior cortical changes in both lenses. Fundus examination showed bilateral, midperipheral 360° reticular-appearing lesions (Fig. 1). Alternate areas of pigment epithelial hypopigmentation and hyperpigmentation formed polygonal reticular units analogous to the meshes of a fishnet. Hyperpigmented 'knobs' were noted at the junction of individual polygonal units as in a net. Within each unit, extensive hypopigmentation of the retinal pigment epithelium and minimal atrophy of the choriocapillaris could be demonstrated by fluorescein angiography (Fig. 2). Fig. 2 also shows linear or sickle-shaped dark areas of hypofluorescence which correspond to zones of hyperpigmentation. Lesions in the posterior pole appeared more confluent and less hyperpigmented, no longer maintaining a reticular appearance as they approached the optic disc. Within the maculae were accumulations of moderately dense black clumps of retinal pigment epithelium (Fig. 3). The retinal vessels and optic discs were normal. Electroretinographic (ERG) responses were nondetectable in both eyes. Because of poor co-operation and a marked reduction in visual acuity, it was impossible to obtain reproducible visual fields, electro-oculogram (EOG), or dark-adaptation studies. The plasma ornithine level was normal (Simmell and Takki, 1973).

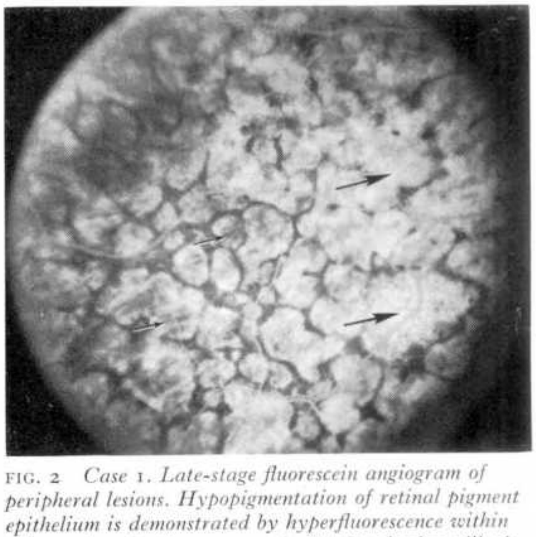


FIG. 2 *Case 1. Late-stage fluorescein angiogram of peripheral lesions. Hypopigmentation of retinal pigment epithelium is demonstrated by hyperfluorescence within polygonal units (large arrows). Patchy choriocapillaris atrophy is demonstrated by retained visibility of large choroidal vessels within some polygonal units (arrows). Also seen are sickle-shaped areas of hypofluorescence*

Address for reprints: Gerald A. Fishman, MD, Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, Illinois 60612, USA

Case 2, a 63-year-old white woman, had a history of progressively failing central vision during the preceding decade and diminishing night vision of approximately 12 years' duration. Visual acuity, documented elsewhere in 1972, was 20/20 in the right eye and 20/30 in the left. At that time, the visual fields were noted to be constricted. Because of a fundus abnormality, her physicians considered the diagnosis of tapeto-retinal degeneration or gyrate atrophy of the choroid and retina.

The patient's father was alleged to have had extremely poor eyesight at the time of his death at the age of 85 years. His ocular problems began at about the age of 55 years with night blindness and decreasing central vision. He was told by an ophthalmologist that he had a 'pigment dispersal'. The patient's elder brother also had markedly reduced vision at the time of his death at the age of 78 years. However, he was a diabetic, and details of his eye disease were not available. Other members of the family, including six other siblings, were not similarly affected. Although her specific recollections were uncertain, the patient stated that she did have Dutch ancestors.

When first examined by us in May 1973 the patient's visual acuity was hand movements at 1 m with correction +3 D sph. in both eyes. External and motility examinations were unremarkable. Both pupils reacted briskly to direct and consensual light stimuli. Slit-lamp biomicroscopy of the anterior segments was normal. Early cortical and nuclear sclerotic changes were seen in both lenses. The vitreous was normal bilaterally. Ophthalmoscopic examination showed that the appearance of both eyes was virtually identical (Fig. 4). Both discs were normal, with a cup-disc ratio of 0·4. The retinal vessels appeared to be normal in calibre and course. There was a scattered mottling of the retinal pigment epithelium within the macular region, especially in the right eye (Fig. 5). The sensory retinal tissue in this region appeared thin on biomicroscopic examination. Approximately 4 disc diameters temporal to the fovea and 1 disc diameter nasal to the disc, discrete reticular pigmentary changes began which extended anteriorly to the equator for 360°. This pattern became confluent and therefore indistinct at the posterior pole. As in Case 1, the reticular changes were formed by alternate areas of decreased and increased density of the retinal pigment epithelium. Areas of increased pigment density circumscribed zones of hypopigmentation creating a polygonal mosaic pattern. These areas were approximately one-half disc diameter in size (Fig. 6). Occasional scattered clumps of pigment were seen in the sensory retina. Fluorescein angiography demonstrated that choriocapillaris vessels were present in areas of clinically evident retinal pigment epithelial hypopigmentation (Fig. 7). Even within the posterior pole, where the reticular pattern was clinically less evident, dark areas of hypofluorescence were apparent where increased pigment density was still present (Fig. 8). No leakage of dye was noted from either the large retinal vessels or the foveal capillaries. Within discrete polygonal lesions, late fluorescein staining of the choroid and sclera both accentuated the reticular pattern of hypopigmentation and emphasized the presence of choriocapillaris vessels (Fig. 9). Visual fields measured on a Goldmann perimeter revealed a 15° relative central scotoma bilaterally. Peripheral fields were irregularly constricted within 30° to 2 isoptres (II-4e and IV-4e). An ERG revealed markedly subnormal photopic and scotopic responses in both eyes. The scotopic b-wave amplitude was only 50 μV in the right eye and 75 μV in the left after 20 min of dark adaptation. (Scotopic b-wave values for her age would normally be greater than 275 to 300 μV in our laboratory.) An EOG showed light-peak to dark-trough ratios of 1·50 bilaterally. These ratios are significantly below 1·70, the lowest limit of normal for the patient's age group. Dark-adaptation studies were unsuccessful because of the patient's marked loss of central vision. A quantitative urine-analysis and plasma determination for amino-acids revealed a normal electrophoretic pattern with no increase in ornithine.

The patient's only child, a 41-year-old son, was examined ophthalmoscopically and found to be normal. Findings on ERG, EOG, and fluorescein angiography were also normal.

Discussion

Previously reported diseases with reticular pigmentary changes of the retina include Sjögren's reticular dystrophy, Mesker's macroreticular dys-

FIG. 1 *Case 1. Reticular-appearing lesions in midperiphery of right eye. Numerous polygonal units are formed by alternate areas of pigment epithelial hypopigmentation and hyperpigmentation. Note knob-like formations at polygonal interfaces (arrows)*

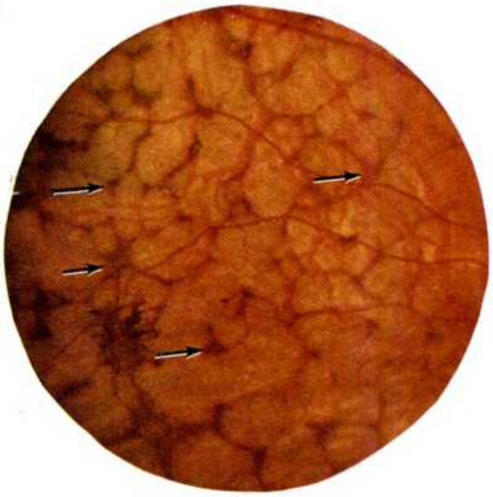
FIG. 3 *Case 1. Posterior pole of right eye. Moderately dense clumps of retinal pigment are seen within macula. Also demonstrated are areas of retinal pigment epithelial hypopigmentation. Disc and retinal vessels are normal*

FIG. 4 *Case 2. Montage from right eye depicting mosaic of polygonal units formed by areas of retinal pigment epithelial hypopigmentation*

FIG. 5 *Case 2. Pigment mottling within right macula. Optic disc and retinal vessels were normal for patient's age. Note areas of retinal pigment epithelial hypopigmentation in perimacular regions (arrows)*

FIG. 6 *Case 2. Reticular changes in midperiphery. As in Case 1, both areas of pigment epithelial hypopigmentation (larger arrows) and hyperpigmentation (smaller arrows) are seen. Although less evident than in Case 1, knob-like formations at intersection of polygonal units are seen*

FIG. 10 *Posterior pole from a patient with Sjögren's reticular dystrophy. Polygonal units formed by mesh of hyperpigmentation. Note knob-like formations at polygonal unit interfaces. Also seen is localized clump of dark retinal pigment within fovea* (courtesy of Dr August Deutman)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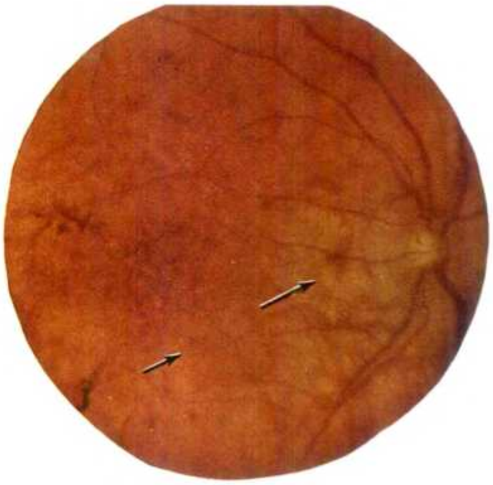
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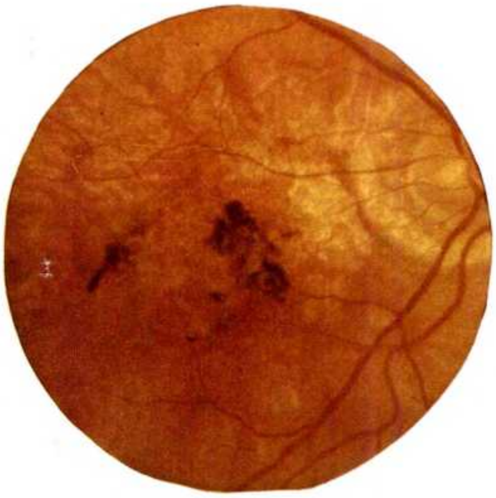
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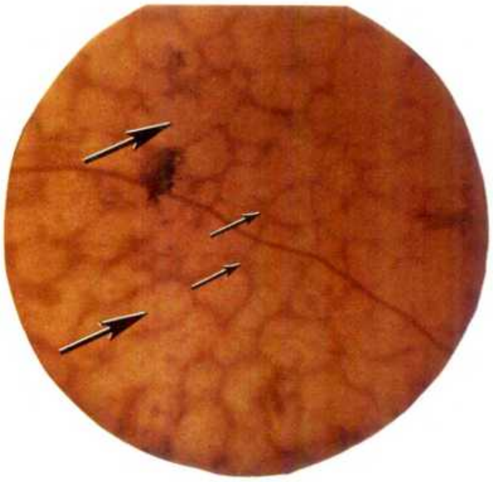
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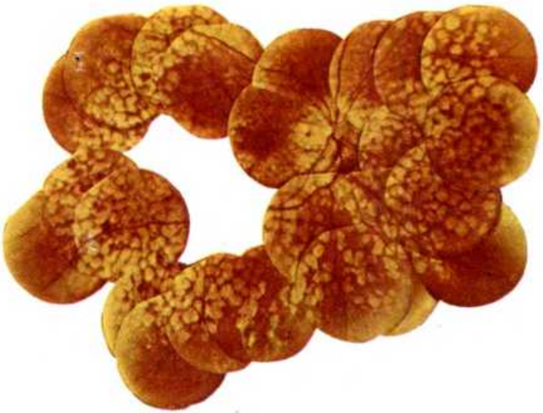
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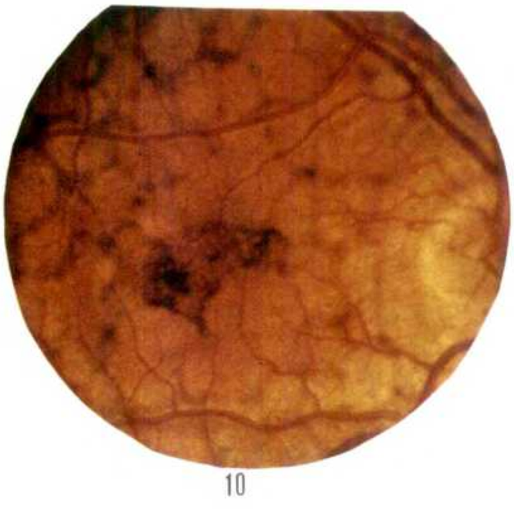
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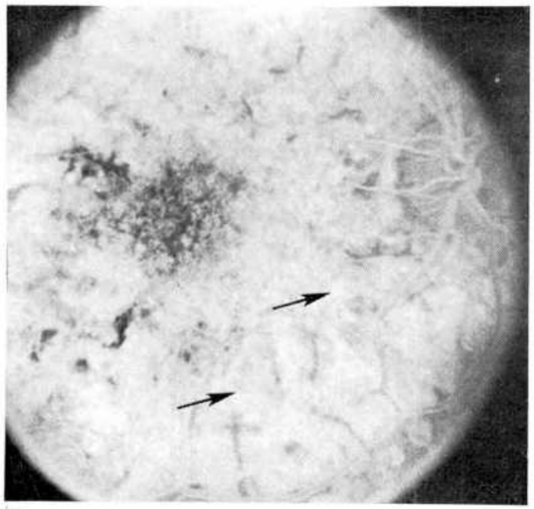

FIG. 7 *Case 2. Fluorescein angiogram from right eye. Hyperfluorescence (arrows) demonstrates anatomical integrity of choriocapillaris vessels within areas of clinically apparent retinal pigment epithelial hypopigmentation*

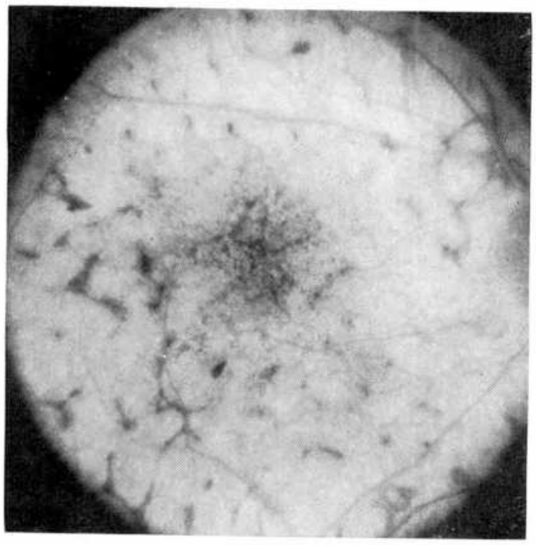

FIG. 8 *Case 2. Late stage angiogram from right eye showing dark patches of hypofluorescence from areas of hyperpigmentation*

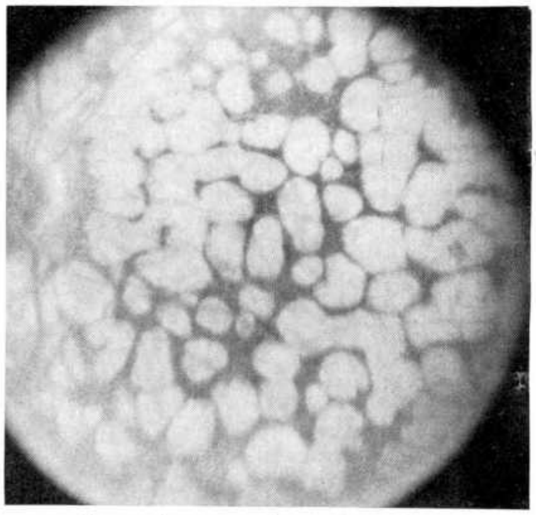

FIG. 9 *Case 2. Late stage fluorescein angiogram from left eye demonstrating staining of choroid and sclera. Staining emphasizes presence of choriocapillaris vessels from which fluorescein dye diffuses*

trophy, and gyrate atrophy of the choroid and retina. Sjögren (1950) first described a reticular dystrophy of the retinal pigment epithelium in eight of 13 children from a Swedish family. Bilateral fundus lesions consisted of a reticular network of black hyperpigmented lines covering most of the posterior pole. Pigmented knobs at the intersection of the dark lines gave the fundus a fishnet appearance. The areas of irregularly-shaped open meshwork, between the hyperpigmented lesions, were approximately one-quarter to one-half disc diameter in size. These areas were not ophthalmoscopically atrophic. Pigmentary changes in the fovea began with a central black spot, surrounded by concentric rings of hyperpigmentation. A foveal light reflex was, however, present. The pigmentary changes were progressive, as the concentric rings of pigment expanded into an initially albinotic-appearing periphery. Visual acuities, peripheral fields, and colour vision were normal. Five of the children had deaf-mutism, and two had spherophakia (Holmgren, 1950).

Similarly affected patients were reported in the Netherlands by Ten Doesschate (1965) and by Deutman and Rümke (1969) (Fig. 10). Visual acuity, peripheral fields, colour vision, ERG, and EOG were normal. Fluorescein angiography heightened the characteristic mosaic pattern and demonstrated a normal choriocapillaris and larger choroidal vessels (Fig. 11). Deutman and Rümke concluded from fluorescein studies that the retinal pigment epithelium between the areas of obvious hyperpigmentation was defectively pigmented. In a later publication, Deutman (1971) emphasized that the areas of hyperpigmentation were deep to the sensory retina, involving the retinal pigment epithelial layer. He also noted that the pigment accumulation tended to fade in later years after spreading peripherally. Apparently, visual acuity diminished only slightly. Deutman concluded that

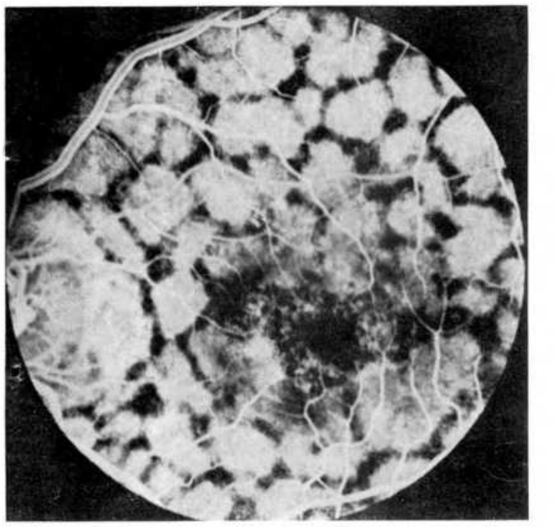

FIG. 11 *Fluorescein angiogram of left eye from patient with Sjögren's reticular dystrophy. Regions of hyperfluorescence result from hypopigmentation of retinal pigment cells* (courtesy of Dr August Deutman)

the fundus abnormality was inherited as an autosomal recessive trait.

Mesker, Oosterhuis, and Delleman (1970) described similar-appearing fundus and fluorescein findings in three patients. A coarse reticular network of pigment bands was described in and around the macula of a 21-year-old woman. Areas of retinal pigment epithelium between the pigmented reticular bands were thought to show an abnormally intense fluorescence on angiography. The choroidal vessels appeared to be normal. The macular area contained some foveal pigmentation while the periphery appeared albinotic. Visual acuity was reduced in two cases and an ERG was subnormal in one patient. Primarily because of a slight difference in pigmentary changes, subnormal ERG and a decrease in visual acuity, these authors felt that their patients represented a different disease from that reported by Sjögren. They applied the term 'dystrophia macroreticularis laminae pigmentosae retinae' to describe the disease in their patients.

We feel that the similarities between Sjögren's (1950) dystrophy and that of Mesker and others (1970) strongly suggest they are the same genetic disease. The latter reported older patients who may have been manifesting more advanced changes as noted by subnormal ERG amplitudes and diminished vision. Two patients (B and C) of Mesker and others (1970) were in their forties, while the oldest patient of Deutman and Rümke (1969) was only 14 years old. Those reported by Sjögren ranged in age from 8 to 33 years (mean 22). Although one patient (A) of Mesker and others (1970) was first examined when aged 21 years, subnormal ERG values were not reported until the fifth decade. Patient B had vision and ERG recordings which we interpret as normal, although Mesker and others (1970) were not definitive in their statement of ERG findings having been 'in accordance with degenerative lesions in the posterior pole'.

Patients with gyrate atrophy of the choroid and retina present with a distinct fundus appearance (Kirstjens, 1965). Within the retina are sharply defined atrophic areas involving the retinal pigment epithelium, sensory retina, choriocapillaris, and larger choroidal vessels. Beginning in the midperiphery, these atrophic areas progress centrally, initially sparing the macular region. The disc and retinal vessels generally remain normal. Sporadic clumping of retinal pigment epithelium can also be noted. Most of these patients complain of night blindness, generally when they are in their 'teens or twenties, antedating any deterioration of central vision. Eventually, central acuity can be severely limited, accompanied by constricted peripheral fields or annular scotomas. The ERG and EOG are frequently subnormal. Many affected patients have associated complicated cataracts at an early age (60 per cent) or high myopia (88 per cent) or both. The absence of both choriocapillaris and larger choroidal vessels within atrophic areas, in addition to the earlier onset of symptoms, distinguishes patients with gyrate atrophy of the choroid and retina from our two cases. Additionally, plasma ornithine determinations were normal (Simmell and Takki, 1973).

The history and ophthalmoscopic appearance of our patients show some similarities to those with the diagnosis of primary diffuse choroidal atrophy (Archer, Krill, and Newell, 1971). Generally, when they are in their thirties, these patients present with either a decrease in visual acuity or, more frequently, poor night vision. In time, there is a relentless, bilateral loss of central vision and a progressive decrease in dark-adaptation function. The ophthalmoscopic appearance includes a diffuse atrophy of both the retinal pigment epithelium and choriocapillaris, rendering the larger choroidal vessels more prominent. The retinal vessels and optic disc are generally normal. Fluorescein angiography of a 49-year-old patient (Fig. 12) with primary choroidal atrophy showed the larger choroidal vessels to be more prominent in the regions of choriocapillaris atrophy. Late connective tissue staining of both the choroid and sclera is absent in those areas in which the choriocapillaris is atrophic. Other areas in which the choriocapillaris is still present appear remarkably

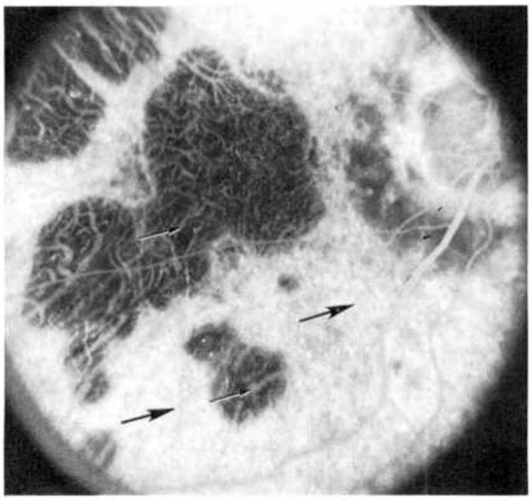

FIG. 12 *Fluorescein angiogram of right eye from patient with primary diffuse choroidal atrophy. Note areas of prominent larger choroidal vessels where choriocapillaris vessels are atrophic (smaller arrows). Normal choriocapillaris vessels are seen as regions of hyperfluorescence (larger arrows)*

similar to the fluorescein pattern noted in our patients. However, we feel that it is unlikely that our patients represent an early stage of choroidal atrophy in which the choriocapillaris is not yet atrophic. In our patients, the markedly abnormal ERG and visual acuity, and their ages attest to the advanced nature of the disease. Even at this advanced stage, choriocapillaris vessels were demonstrable on fluorescein angiography. This feature facilitates the distinction between our patients and those with primary choroidal atrophy.

The fundus abnormalities in our cases show remarkable similarities to those reported in Sjögren's reticular dystrophy. Common to both groups are hyperpigmented interlacing polygonal lines which circumscribe areas of hypopigmented retinal pigment epithelium and show knob-like processes at points of intersection. Neither markedly diminished vision nor diminished ERG amplitude was previously considered to occur in Sjögren's reticular dystrophy. Our cases suggest that patients with this disease may eventually manifest secondary diffuse photoreceptor abnormalities. The retinal changes may therefore not be as benign as initially considered.

Since we were unable to document the presence or absence of typical early lesions of Sjögren's dystrophy in either of our patients, we must accept the possibility that the reticular tapeto-retinal dystrophy described in this report is simply a phenocopy of Sjögren's dystrophy. Until this uncertainty is resolved, we suggest a note of caution regarding the ultimate visual prognosis in Sjögren's reticular dystrophy.

Summary

Findings from two patients with a reticular tapeto-retinal dystrophy strongly suggested advanced stages of Sjögren's reticular dystrophy. These observations emphasize that, although initially a benign disease, advanced stages of Sjögren's dystrophy may eventually manifest diffuse photoreceptor and retinal pigment epithelial disease.

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Vitreous opacities in primary amyloid disease
A clinical, histochemical, and ultrastructural report

ROGER A. HITCHINGS AND RAMESH C. TRIPATHI*
Moorfields Eye Hospital and Department of Pathology,
Institute of Ophthalmology (University of London)

Severe loss of visual acuity due to vitreous opacities may result from haemorrhages, inflammatory and degenerative conditions, tumour cells, or amyloid–the last being rare (Duke-Elder, 1969; Jaffe, 1969). It is important, however, to recognize amyloid disease as being a cause of vitreous opacities, because most previously reported cases have been patients with familial amyloidosis, a systemic disease of protean manifestations with a poor prognosis. Sporadic cases of systemic amyloidosis with vitreous opacities have also been reported (see Table).

Patients with systemic amyloid disease may initially present with visual symptoms due to vitreous opacities. These opacities usually have a characteristic appearance thus enabling the ophthalmologist to suggest the correct diagnosis.

The purpose of this paper is to report three patients of primary amyloid disease, who initially presented to the ophthalmologist with slow deterioration of their visual acuity. The diagnosis was suggested by the appearance of the vitreous opacities and confirmed initially by conjunctival biopsy in two of the three cases and subsequently by histological examination of the vitreous in all three cases. To our knowledge, this is the first British report of vitreous opacities in primary amyloid disease.

Case reports

CASE 1

A 53-year-old Caucasian woman initially presented at another hospital in December 1970 with a history of progressive loss of visual acuity during seven years in her right and five years in her left eye. There was no history of systemic or ocular disease, nor were her visual symptoms precipitated by trauma. There was no relevant family history of ocular or systemic illness. At that hospital she underwent an extracapsular lens extraction and partial vitrectomy in her right eye.

On examination at Moorfields Eye Hospital in January 1971, her visual acuity in the right eye was perception of light, and in the left eye hand movements. The right eye showed evidence of a broad iridectomy and an extracapsular lens extraction. The posterior vitreous was opaque. The left eye had a normal anterior segment with a clear lens. On the posterior lens surface there were multiple white circumscribed opacities in the form of 'pseudopodia lentis'; from each opacity an opaque strand could be traced posteriorly, through a region of clear vitreous, to enter a greyish-white meshwork of vitreous opacities (Figs 1 and 2). No view of the fundus could be obtained in either eye.

The following investigations were carried out: chest *x* ray, haemoglobin (Hb), white blood count (WBC), erythrocyte sedimentation rate (ESR), electro-oculogram (EOG) and electroretinography (ERG)—all of which were within normal limits. Electrophoresis of serum proteins, however, revealed an elevated α_2 globulin.

In January 1971, a right vitrectomy by the 'open sky' technique (Kasner, Miller, Taylor, Lever, and Norton, 1968) was performed. Subsequent examination of the fundus failed to reveal any abnormality. One month later the retina totally detached and remained so, despite attempts at surgical management; the eye subsequently became phthisical. In January 1972, prophylactic encircling cryotherapy was carried out on the peripheral retina of the left eye. A diagnostic conjunctival biopsy was performed for histopathological and electron microscopical examination. In March 1972, a left vitrectomy was performed, again using the 'open sky' technique and the material was processed for light and electron microscopical examinations. Postoperatively, as far as the fundus could be seen, it appeared to be normal. However, it became obscured by an increase in the vitreous opacities during the next 4–6 weeks and was followed by a gradual onset of bullous keratopathy.

After ophthalmological examination and conjunctival biopsy, the patient was referred for a general medical examination which revealed a peripheral neuropathy and carpal tunnel syndrome, attributable to systemic amyloid disease.

It has not proved possible to examine other members of the family.

CASE 2

A 54-year-old Caucasian man presented with a 10-year history of progressive bilateral loss of visual acuity. In September 1971, he was admitted to another

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*Address for reprints: R. C. Tripathi, MD, PhD, Institute of Ophthalmology, Judd Street, London WC1H 9QS

Table *Vitreous opacities in primary amyloid disease—a review of the literature*

Author	*Year*	*Cases (no.)*	*Age (yrs)*	*Sex*	*Duration of loss of visual acuity (yrs)*	*Clinical appearance of vitreous opacities*	*Other ocular features*	*Histological examination*		*Family history*
								Vitreous	*Other organs*	
Falls and others (Cases 1 and 2 Kantarjian and de Jong, 1953)	1955	4 (1)	24	Female	3	Many dense sheet- or film-like opacities	Dilated fixed pupils reacting only to accommodation Pin-point to plaque-like grey deposits, with occasional intravitreal extension, on many peripheral arterioles Exophthalmos	—	Perivascular amyloid at necropsy	Cases 1 and 2 were sisters Father died from amyloidosis; his ocular findings included proptosis, aniscoria, and no pupillary light response
		(2)	23	Female	More than 1	Dense web or sheet-like opacities attached by footplates to disc and retinal surface	Aniscoria, reacting only to accommodation Proptosis Grey deposits on retinal arterioles	—	—	
		(3)	50	Male	4	Sheets of semi-opalescent hyaline opacities, attached in places to the retina	Anisocoria, normal pupillary reactions Bead-like deposits on retinal vessels	—	Positive gingival biopsy: autopsy demonstration of diffuse amyloid	22-yr-old son had patchy grey sheathing on retinal arterioles
		(4)	47	Male	3	Hyaline sheet-like opacities Left vitreous clear at time of initial examination	Normal pupillary size and reaction Semi-opalescent beads of hyaline material on posterior lens surface right eye Similar deposits on retinal arterioles	—	Negative gingival biopsy Positive skin biopsy	Cousin of Case 3
Chambers, Medd, and Spencer	1958	1	33	Male	2	Vitreous opacities in left eye	Irregular pupils reacting to convergence but not to light 1 yr later, pupils reacted neither to light nor convergence	—	Positive interdigital nerve and gingival biopsies Extensive amyloid involvement at autopsy	
Kaufman and Thomas	1959	2 (1)	77	Male	7 right eye 2 left eye	Glass-wool opacities in each eye	Normal pupils	Positive for amyloid	Positive skin, gingiva, and muscle biopsies	Brother died from systemic amyloidosis aged 74 yrs Anisocoria noted before death
		(2)	62	Male	13 right eye 6 left eye	Sheet-like vitreous opacities Asymmetric involvement right more than left eye	Normal pupils 'Periphlebitis' and 'arteritis' in left eye 2 yrs previously	Positive for amyloid	Positive gingival biopsy	3 younger brothers have primary amyloidosis
Schlesinger and others	1962	1	63	Male	10	Unilateral opacities, 'yellow pencil shavings' in right eye	Bilateral ptosis Perivascular opacity in left eye	—	Positive muscle biopsy	19 other family members had peripheral neuropathy No vitreous opacities noted
Delank, Koch, Könn, Missmahl, and Skwelack	1965	2 (1)	27	Female		Grey cobwebby opacities precluding any fundal view Asymmetric involvement right more than left eye	Anisocoria, poor light and near response	—	Positive rectal mucosa, skin and lymph node biopsies	
		(2)	24	Female		Unilateral cobweb opacity	—	—	—	
Duke and Paton (Case 1, Kaufman, 1958)	1965	1	31	Male	10	Large 'cells' in anterior vitreous, with veil-like opacities peripherally and posteriorly	Normal pupils	Positive for amyloid	Positive lymph node and skin biopsies	Mother and sister had amyloid disease

						7 yrs later opacities had increased in density and were whitish-yellow No view of fundus in either eye				
Wong and MacFarlane	1967	1	19	Female	—	Vitreous veil and of a glass-wool appearance, arising from a retinal vessel in each eye	Anisocoria with right mydriasis, and non-reactive to light and accommodation: left normal Keratoconjunctivitis sicca-like findings	Positive vitreous at necropsy	Positive gingiva, muscle and nerve biopsies Extensive systemic involvement at autopsy	Known case of familial amyloidosis
Crawford	1967	1	36	Male	—	Slight intravitreal extension of a greyish para-arteriolar lesion		Negative vitreous at necropsy	Positive liver biopsy Widespread amyloid deposits at necropsy	Sporadic case of primary amyloidosis
Kasner and others	1968	2 (1)	67		—	Veil-like opaque grey strands		Positive congo red material	Positive congo red deposits Negative rectal and mucosal biopsies Positive rectal biopsy	Sporadic cases of primary amyloidosis
		(2)	62		—			Positive congo red material Positive on electron microscopy		
Andersson and Kassman	1968	3 (1)	63	Female	10	Bilateral sheet-like opacities	Anisocoria, sluggish light reflexes	—	Positive sural nerve biopsy	
		(2)	43	Male	—	Bilateral opacities	—	—	—	Brother of Case 1, died 10 yrs later 3 other brothers had a peripheral neuropathy 3 other relatives had symptoms suggestive of a peripheral neuropathy
		(3)	60	Female	Less than 1	Band-like opacities in right eye, anterior vitreous and reticular preretinal opacities 9 months later right fundus could not be seen because of increased density of vitreous opacities	Normal pupil size and normal reflexes Left eye normal when first seen 'Incipient amyloid deposits', 9 months later	—	Positive sural nerve biopsy	
Hamberg	1971	2 (1)	51	Male	2	Bilateral opacities, like precipitated albumins	—	—	—	—
		(2)	53	Male	—	Bilateral opacities, like precipitated albumins	—	Positive for amyloid at necropsy	Widespread amyloid deposition	Brother of Case 1 Sister noted to have similarly appearing opacities
Hitchings and Tripathi	1976	3 (1)	53	Female	7 right eye 5 left eye	Bilateral linear meshwork of opacities with pseudopodia lentis	—	Positive for amyloid on histology and electron microscopy	Positive conjunctival biopsy	No family members examined
		(2)	54	Male	10	Bilateral linear meshwork of opacities with pseudopodia lentis	Sluggish pupillary reaction to light and accommodation	Positive for amyloid on histology and electron microscopy	Positive conjunctival biopsy Positive radial nerve biopsy	No family members examined Died but necropsy not permitted
		(3)	60	Female	4	Bilateral linear meshwork of opacities with pseudopodia lentis		Positive for amyloid on histology	—	No family members examined

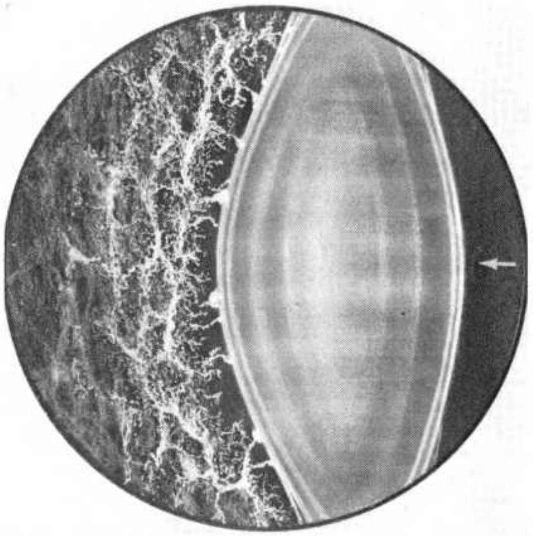


FIG. 1 *Case 1. Left eye. Artist's impression showing meshwork of linear vitreous opacities attached to posterior lens surface by footplates (pseudopodia lentis)*

hospital for investigation where his visual acuity was recorded as 6/24 right eye and counting fingers left; bilateral vitreous opacities were noted. Examination of the fundus in the right eye showed no abnormality, but the fundus could not be seen in the left eye. Neither he nor his family had any history of ocular or medical disease. Further loss of visual acuity occurred and he was transferred to Moorfields Eye Hospital in February 1972.

On examination, his visual acuity was 6/60 right eye, counting fingers left. His visual fields were full to a 10 mm white target. The ERG and EOG did not reveal any abnormality. Each anterior segment was normal. The pupils were equal in size but with sluggish light and near reactions. The intraocular pressures were normal. The lens in each eye was clear but there were multiple circumscribed greyish-white opacities on the posterior surface of each lens (Figs 3 and 4) and from each opacity an opaque fibril ran posteriorly, through a relatively clear zone, to join a meshwork of vitreous opacities. No view of either fundus was possible. Amyloid disease was suspected and although the conjunctiva appeared to be normal, a diagnostic conjunctival biopsy was performed.

The patient was referred for a general medical examination which revealed a peripheral neuropathy,

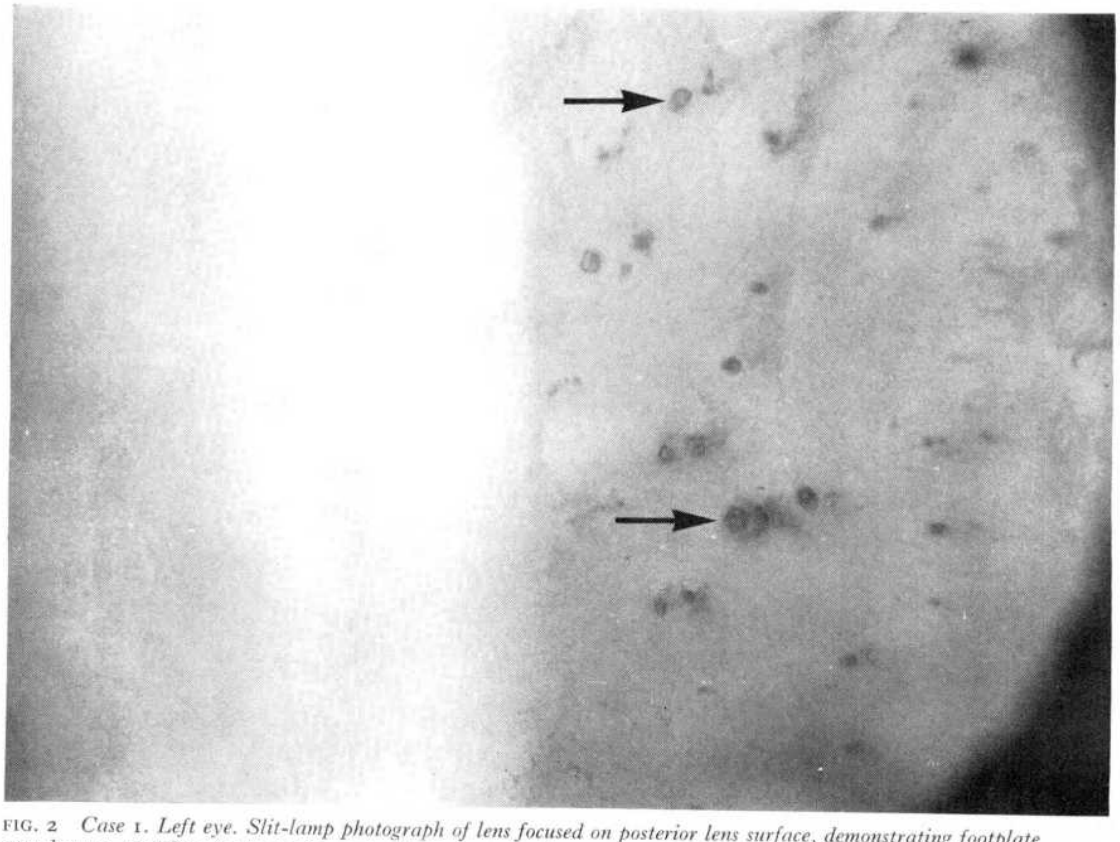


FIG. 2 *Case 1. Left eye. Slit-lamp photograph of lens focused on posterior lens surface, demonstrating footplate attachments, pseudopodia lentis (arrow), of vitreous opacities*

orthostatic hypotension, and an abnormal sweating pattern. Biopsy of the left superficial radial nerve was performed which showed perineural deposits of amyloid together with degenerative changes in the nerve fibres. No abnormality, however, was detected on chest *x*-ray examination; blood analysis for Hb, WBC, ESR, and serum proteins was also normal. There was no Bence-Jones protein in the urine.

In September 1972, the patient underwent prophylactic encircling peripheral retinal cryotherapy followed by an 'open sky' vitrectomy (Kasner and others, 1968) to the right eye 2 months later. The vitreous material thus being available was examined by light and electron microscopy. In July 1973 he underwent a 6·5 mm penetrating keratoplasty for bullous keratopathy. Histopathological examination of the corneal disc revealed features of Fuchs's dystrophy but no deposits of amyloid.

In September 1973 he developed renal failure and despite intensive care he died. Permission for necropsy examination was not given.

It has not proved possible to examine other members of his family.

CASE 3

A 60-year-old Caucasian woman presented in 1967 with a 12 month history of 'cobwebs' in front of both eyes. At that time she was being treated for low blood pressure. The features of her vitreous opacities have been reported elsewhere (Law, 1971). Neither she nor her family had any history of ocular or systemic disease.

On examination, her visual acuity was 6/9 right eye and 6/6 left. The anterior segments and intraocular pressure were normal in each eye. The lens in each eye was clear. Multiple circumscribed white opacities were, however, present on the posterior surface of each lens and from these greyish-white fibrillar opacities extended posteriorly to join an extensive meshwork of opacities in the central vitreous (Fig. 5). No fundal abnormality could be detected in either eye.

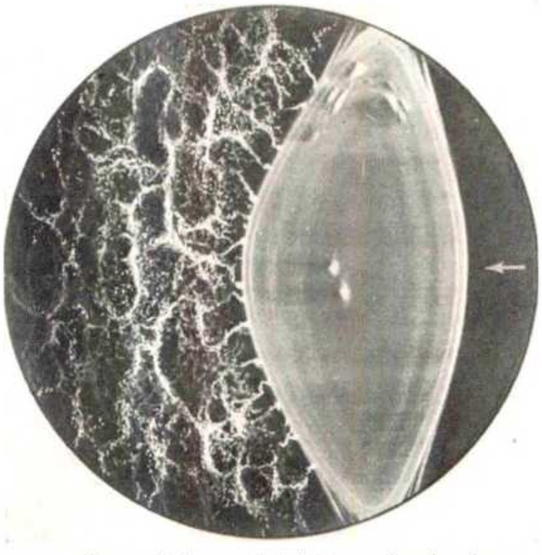


FIG. 3 *Case 2. Left eye. Artist's impression showing a meshwork of linear opacities attached to posterior lens surface by footplates (pseudopodia lentis)*

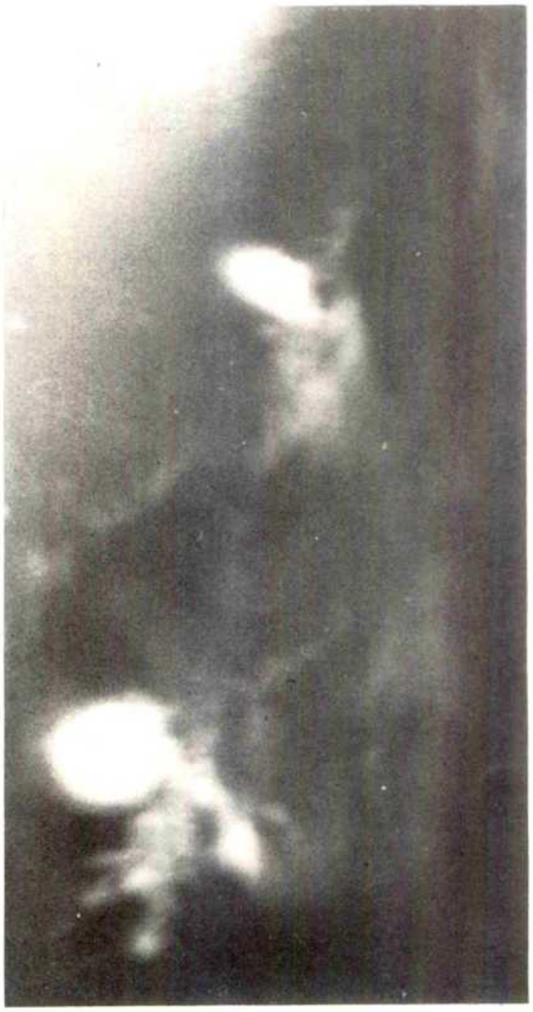


FIG. 4 *Case 2. Left eye. Macrophotograph showing two 'footplate' vitreous opacities on posterior lens surface, each with linear vitreous opacities passing posteriorly into vitreous cavity*

Because of bilateral loss of visual acuity, several months later she attended another hospital and underwent bilateral vitrectomy; a diagnosis of amyloidosis of the vitreous was made.

Histopathology and ultrastructure

Conjunctival biopsies (10 × 8 mm) were obtained from the lower fornix (Cases 1 and 2) under local amethocaine anaesthesia. The specimens were divided into two pieces; one piece of each specimen, intended for conventional light microscopy and

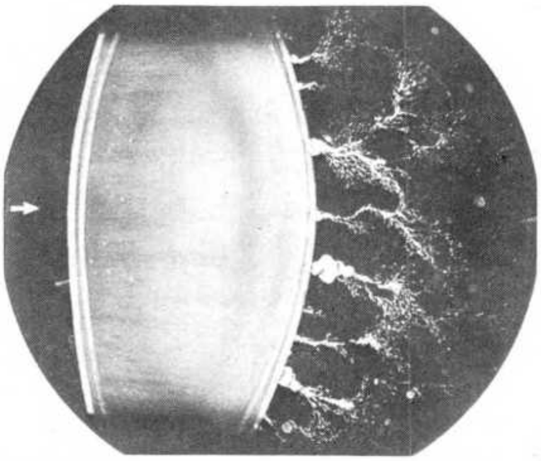


FIG. 5 *Case 3. Left eye. Artist's impression showing linear vitreous opacities attached to posterior lens surface by footplates (pseudopodia lentis)*

histochemical studies, was fixed in formol saline and embedded in paraffin wax; sections were stained with haematoxylin and eosin, congo red, periodic acid-Schiff, crystal violet, toluidine blue, and thioflavine T. The other piece of each specimen was fixed in veronal acetate buffered osmium tetroxide, dehydrated through ascending grades of ethanol, and was finally embedded in Araldite. Sections were cut with glass knives on a LKB ultramicrotome; semi-thick sections (1 μm) were stained with toluidine blue for block orientation and examination by light microscopy. Thin sections (70–90 nm) were stained with uranyl acetate (alcoholic or aqueous) and aqueous lead citrate, and electron micrographs were taken using AEI EM6 and Joel 100C electron microscopes.

Similarly, vitreous specimens taken at the time of vitrectomy from both cases, were processed for conventional histological examination and electron microscopy. Some vitreous material was also spread directly on glass slides as a smear and this was stained with haematoxylin and eosin, congo red, crystal violet, and thioflavine T.

The lens from Case 1 was fixed in formol saline, embedded in celloidine and sections were stained for light microscopy as described for the conjunctival specimens. The posterior half of the lens from Case 2 was dissected out, and the tissue blocks were fixed in osmium tetroxide and processed for electron microscopy.

CONJUNCTIVA

Light microscopy and histochemistry

An amorphous, eosinophilic, hyaline extracellular material was seen around the vessels, particularly around the veins and lymphatics (Fig. 6). In Case 2, the deposits were also seen immediately beneath the conjunctival epithelium. The deposits stained positively with periodic acid-Schiff and congo red, metachromatically with crystal violet, and khaki colour with van Gieson; to some extent they were autofluorescent but this was greatly enhanced after staining with thioflavine T (Fig. 7). When viewed by polarized light, the congo red positive material showed birefringency and green dichroism, These histochemical findings are characteristic of amyloid (Missmahl, 1957; Vassar and Culling, 1959; Puchtler, Sweat, and Levene, 1962; Cooper, 1969; Pearse, 1972; and others).

Ultrastructure

Electron microscopy generally confirmed the location of the amyloid material seen by light microscopy (Figs 8 and 9). The deposits were variably sized clumps of fine, interlacing, non-branching fibrils. In uranyl acetate and lead citrate stained sections, the individual fibrils were 7–10 nm in diameter; longitudinally-cut fibrils showed two laterally-aligned filaments approximately 3 nm in diameter with an intervening space of approximately 3 nm. The filaments had a beaded appearance repeating at approximately 4 nm. These features are consistent with the electron microscopical appearance of amyloid (Boeré, Ruinen, and Scholten, 1965; Shirahama and Cohen, 1965, 1967; Gueft, Kikkawa, and Hirschl, 1968; Sorenson and Finke, 1968; and others). The ground substance was relatively electron lucent.

In Case 2 wherein subepithelial deposits were seen, the basement membrane was intact and there was no infiltration of the amyloid material into the epithelium.

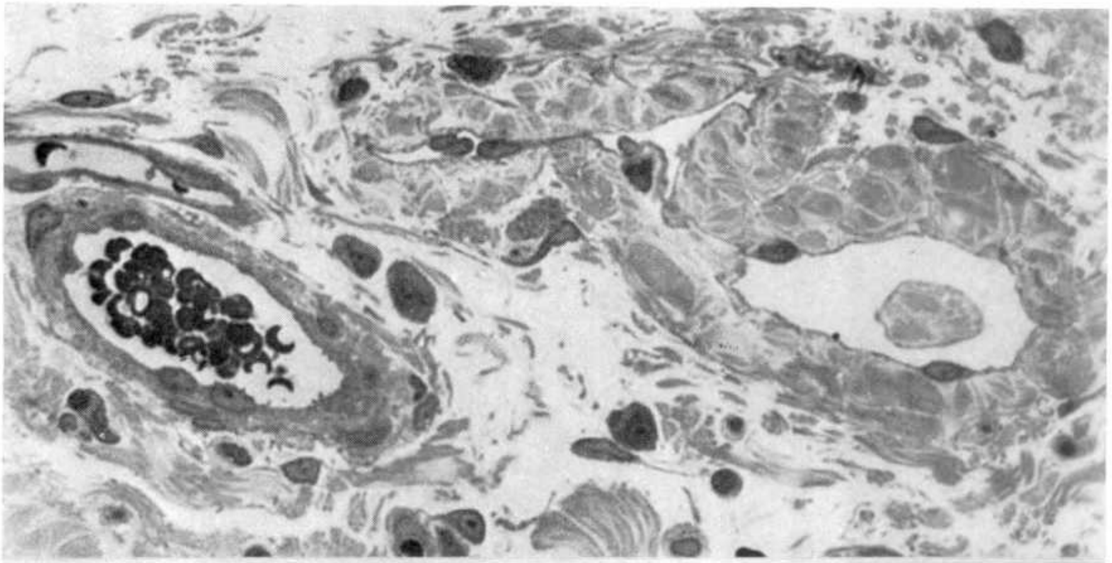
VITREOUS

Light microscopy and histochemistry

Smears and sections of the vitreous from Cases 1 and 2 showed fine and coarse meshworks which stained positively with periodic acid-Schiff and congo red, and metachromatically with crystal violet. Under polarized light, haematoxylin and eosin sections showed birefringency and congo red stained sections additionally showed a green dichroism (Figs 10a and b). The vitreous material from Case 3 was also reported as showing histochemical features of amyloid deposits.

Ultrastructure

Thin sections of the vitreous opacities from Cases 1 and 2 stained with uranyl acetate and lead citrate



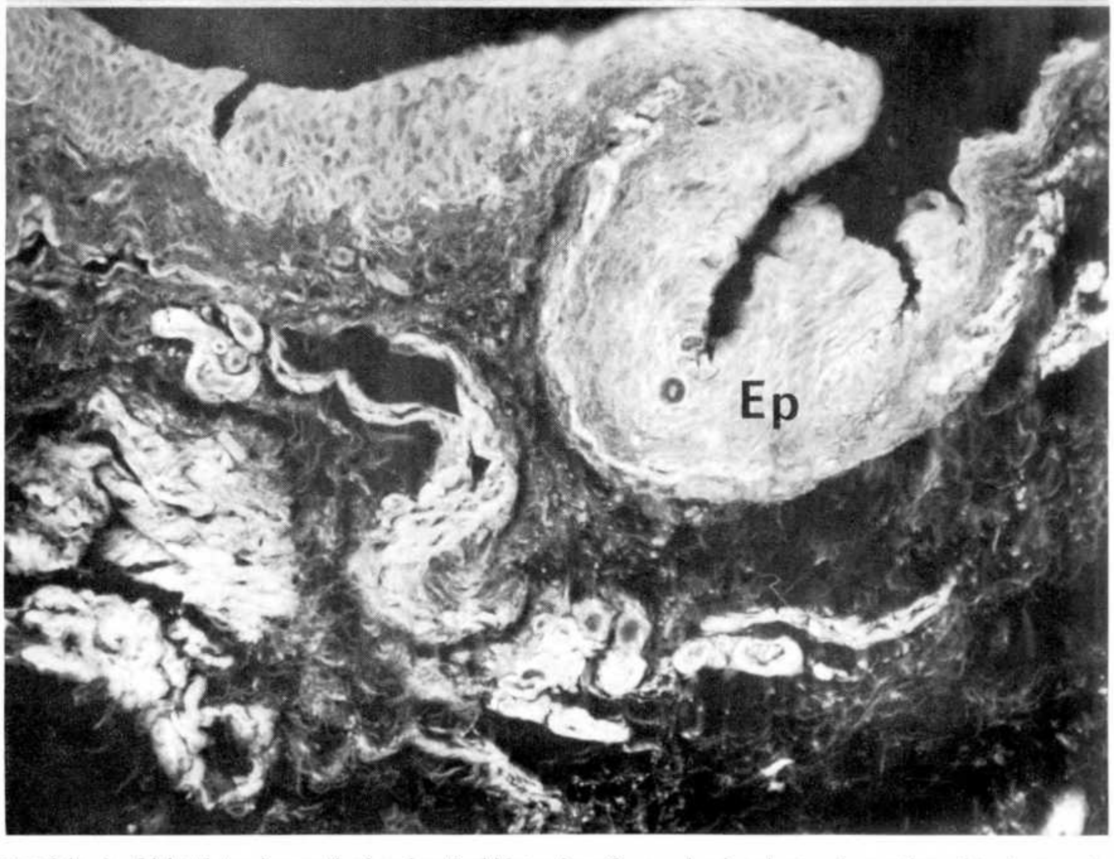


FIG. 6 (top) *Light photomicrograph of conjunctival biopsy from Case* 1 *showing clumps of amorphous deposits around vessels.* × 660

FIG. 7 (bottom) *Light photomicrograph of conjunctival biopsy from Case* 2. *Section was stained with thioflavine T and viewed by ultraviolet light. Intensely fluorescent deposits are seen beneath conjunctival epithelium (Ep) and around blood vessels and lymphatics in conjunctival stroma.* × 220 showed the predominantly fibrillar nature of the material (Fig. 11). The detailed morphology of the individual fibrils was similar to that described for the conjunctival deposits. No cells were seen in the sections examined.

LENS

Light microscopy of Case 1 showed a smooth posterior lens surface and the capsule appeared to be normal. Similarly, semi-thin Araldite sections of the lens from Case 2 showed a smooth posterior lens surface; there was no evidence of the remains of attachment of pseudopodia lentis seen clinically.

Discussion

A summary of cases with systemic amyloid disease and vitreous opacities reported in the literature is set out in the Table. Some cases have appeared in more than one report; we have included only the most recent report to allow a better appreciation of the long-term history of the disease. Most were proved cases of heredo-familial amyloidosis. A peripheral neuropathy was a common feature in affected families, but the incidence of vitreous opacities was reported less frequently.

Previously reported cases usually had a long history of visual loss before the correct diagnosis had been established (Table) and indeed in one case, there was no evidence of systemic disease at the time vitreous opacities were first noticed (Kaufman and Thomas, 1959). Thus visual symptomatology could be the reason for initial presentation, as is also apparent from our patients. Loss of visual acuity in both eyes may not, however, be of equal duration and in a few reports, one eye was apparently normal at first examination (Schlesinger, Duggins, and Masucci, 1962; Andersson and Kassman, 1968).

The vitreous opacities characteristically had a linear structure, descriptions of 'sheet like', or 'band like' opacities being common (see Table). In those cases where the fundus could be seen, opacities were said to be in contact with the retina and retinal vessels through footplates (Falls, Jackson, Carey, Rukavina, and Block, 1955; Wong and MacFarlane, 1967). Similar footplates were seen in the anterior vitreous in contact with the posterior lens surface (Falls and others, 1955; Kaufman and Thomas, 1959). Vitreous opacities in contact with the posterior lens surface were noted in two cases described by Vogt (1942) although he did not suggest amyloidosis as being a cause; one of the patients had 'chronic tuberculosis'. The development of opacities in a previously clear vitreous was noted in one case (Andersson and Kassman, 1968), while a marked increase in the density of the opacities together with a reduction in visual acuity has been reported by several authors (Duke and Paton, 1965; Andersson and Kassman, 1968).

The clinical features of previously published cases are similar, suggesting that slowly progressive visual deterioration apparently caused by linear vitreous opacities with footplate attachments to the retina or posterior lens surface are diagnostic of amyloid disease.

Vitreous opacities in amyloid disease must not be confused with those resulting from more common causes—haemorrhage, inflammation, degeneration, or neoplasms. Opacities associated with amyloid disease may be uniocular, or asymmetric in the involvement of the two eyes. In addition, examination of the apparently normal eye has revealed perivascular greyish opacities on the retinal vessels (Schlesinger and others, 1962).

Pupillary abnormalities were a common ocular complication in many patients with vitreous opacities. The abnormalities were anisocoria, and the failure to react to light and accommodation. In addition a few cases had perivascular exudates; one was a histologically confirmed case of amyloid (Wong and MacFarlane, 1967), but another, of similar appearance, turned out to be a cytoid body (Crawford, 1967).

The diagnosis of systemic amyloidosis is usually confirmed by biopsy; skin, gingiva, rectum, liver, kidney, spleen, respiratory tract, and sternal puncture have all been used (Cohen, 1967). Ease of access and haemostasis have made the gingiva and rectum the two main sites. Positive biopsies for amyloid were obtained in 31 of 32 cases of systemic amyloidosis (Missmahl, 1968). The conjunctiva has not been considered a suitable site, perhaps because it retains normal appearance in systemic amyloidosis (Duke-Elder, 1965; Brownstein, Elliott, and Helwig, 1970). The positive conjunctival biopsies obtained in Cases 1 and 2, despite a normal clinical appearance of the conjunctiva, suggests that microscopic deposition of amyloid could frequently occur. The conjunctiva should be considered as a biopsy site for diagnostic confirmation of systemic amyloid disease (Tripathi and Ashton, 1976).

The origin of amyloid material in the body is not clear. Amyloid comprises three types of protein complexes, types A, B, and possibly C (Benditt, Erikson, Hermodson, and Ericsson, 1971). Type A is found in a perireticulin distribution, secondary to chronic sepsis or an inborn error of metabolism. Type B is mainly found in a pericollagen distribution secondary to myelomatosis and other paraprotein disorders, while Type C occurs with amyloid formed locally with certain tumours. Familial amyloid may involve either Type A or Type B (Hobbs, 1973).

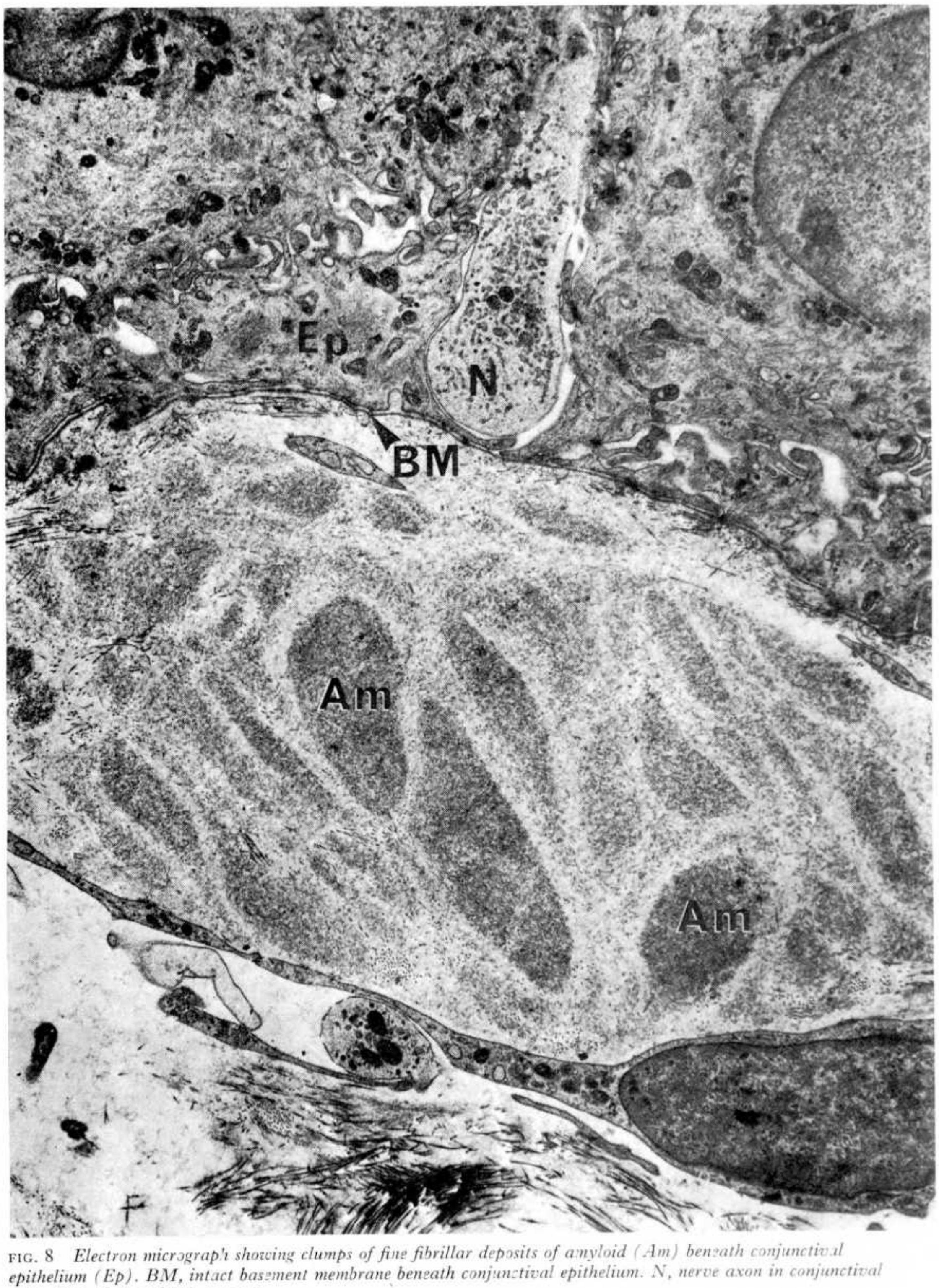


FIG. 8 *Electron micrograph showing clumps of fine fibrillar deposits of amyloid (Am) beneath conjunctival epithelium (Ep). BM, intact basement membrane beneath conjunctival epithelium. N, nerve axon in conjunctival epithelium. UA and LC* × 1250

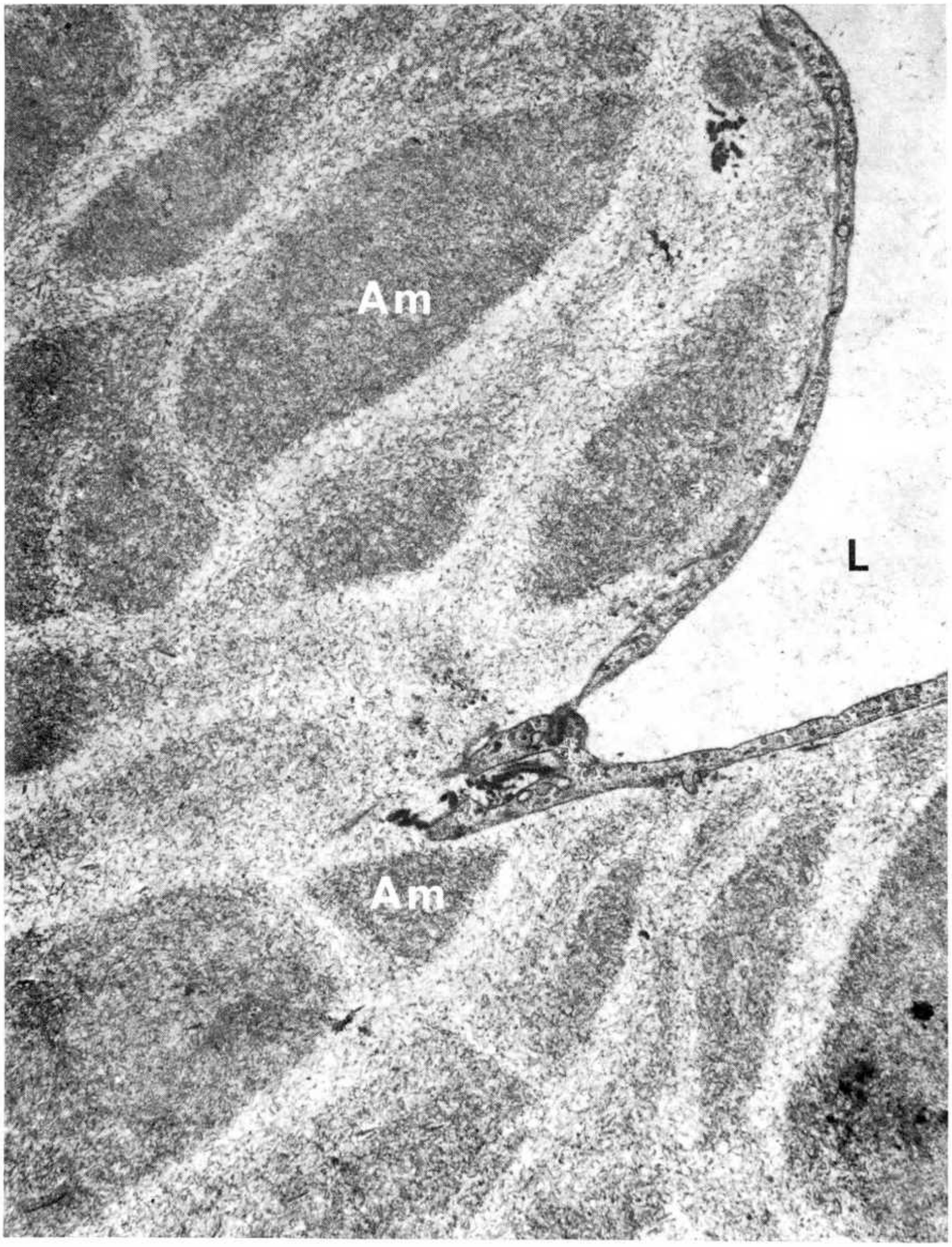


FIG. 9 *Electron micrograph showing perilymphatic deposits of clumps of amyloid fibrils (Am). L, lumen of lymphatic. UA and LC* × 15 000

Recent work on sequential amino-acid analysis suggests that amyloid–B is derived from part of a circulating immunoglobulin protein, itself derived from plasma cells (Glenner, Harbough, Ohms, Harada, and Cuetracas, 1970; Glenner, Terry, Harada, Isersky, and Page, 1971; Glenner, Terry, and Isersky, 1973). In the case of occult or overt plasma cell dyscrasias, this protein appears to be the variable front-half of a light chain (the variable light portion) of an immunoglobulin. It has been suggested that phagocytic cells ingest this circulating protein and deposit amyloid fibrils (Glenner and others, 1973). In one series, 33 out of 40 patients with 'primary amyloid' were found to have malignant lymphoreticular disease (Hobbs, 1973).

Amyloid A protein has amino-acid sequences which are different from known immunoglobulin sequences. Neither their origin nor their precursor, however, is known (Hobbs, 1973).

The site of deposition of amyloid fibrils may depend on three main factors (Glenner and others, 1973). First, it depends on local variations in the rate of formation of the fibril precursor and its removal. Secondly, it depends on the nature of this precursor—for example, small molecules could penetrate capillary walls while larger ones precipitate in capillary lumens. In addition, its precursor may have relative tissue affinity (Ossermann, Takatsuku, and Talal, 1964). Thirdly, there may be a special relationship between the precursor synthesizing cell and the amyloid producing cell. The plasma cells producing a circulating precursor would give rise to systemic amyloid, while a localized plasma cell alone with adjacent histiocytes might produce localized amyloid deposits.

Systemic amyloid deposits secondary to an inflammatory process can resolve following removal of this process (Lowenstein and Gallo, 1970; Hobbs, 1973). In primary amyloid disease the turnover rate would appear to be very slow, allowing accumulation of masses of amyloid material. Intravitreal amyloid deposits could occur after permeation of the precursor across the blood–aqueous barrier, to be converted possibly by intravitreal phagocytes into amyloid fibrils. The linear deposition of amyloid material may result from initial deposition around pre-existing collagen fibrils in the vitreous cavity.

The question arises why only a proportion of patients with systemic amyloid disease develop vitreous opacities. This may be due to one of several factors. All patients may develop opacities in time or, since the disease has a poor prognosis, the patient may succumb from renal or cardiac complications before ophthalmic complications become manifest. There may be variations in the chemical composition of the amyloid protein or in its circulating precursor from case to case. Finally, local factors, such as the state of the intravitreal collagen framework, or the presence of phagocytic cells in the vitreous cavity, may also play an important role.

There is no known treatment for primary amyloid disease. Possible therapeutic attacks could be against the precursor secreting cell, the circulating immunoglobulin, or the amyloid material (Glenner and others, 1973). Cases where plasma cell abnormalities can be demonstrated could be attacked with immunosuppressive drugs and this has been tried with variable results (Missmahl, 1968; Barth, Willerson, Waldmann, and Decker, 1969; Jones, Hilton, and Hobbs, 1972). Immunoabsorbents against the circulating immunoglobulin are a possibility (Glenner and others, 1973). The mobilization of amyloid deposits that occurs after removal of the stimulus shows that the fibril deposition is not irreversible, and a possible method of attack has been suggested by the demonstration that phagocytosis of amyloid fibrils occurred after treatment of the fibrils with specific antisera (Zucker-Franklin, 1970).

Finally, the direct surgical approach has been tried, and there have been several reports of vitrectomy (Duke and Paton, 1965; Kasner and others, 1968). Our experience in Case 1 suggested that despite removal of amyloid material, the opacities returned after several months: thus removal of opacities is not equivalent to cure; in any case these patients have a poor prognosis as is apparent from many reported cases, and this fact must be borne in mind when contemplating major ophthalmic surgery.

Summary

Three patients who initially presented to the ophthalmologist with a history of gradual deterioration of visual acuity showed, on biomicroscopic examination, a linear meshwork of opacities in the vitreous attached to the posterior surface of the lens in the form of pseudopodia lentis. Amyloidosis of the vitreous associated with systemic amyloid disease was diagnosed because of the characteristic nature of the opacities. This was confirmed initially in two of the cases by light and electron microscopical examination of a biopsy of the clinically normal conjunctiva, subsequently by systemic investigations, and finally, by direct histochemical and elecron microscopical examination of the vitreous which became available after vitrectomy in all three cases. It was not possible to examine other members of the families. The relevant literature on vitreous amyloidosis is reviewed in relation to our own findings and the importance of a diagnostic conjunctival biopsy is emphasized. This paper is the first British report on primary vitreous amyloidosis. The pathogenesis of vitreous amyloid opacities is

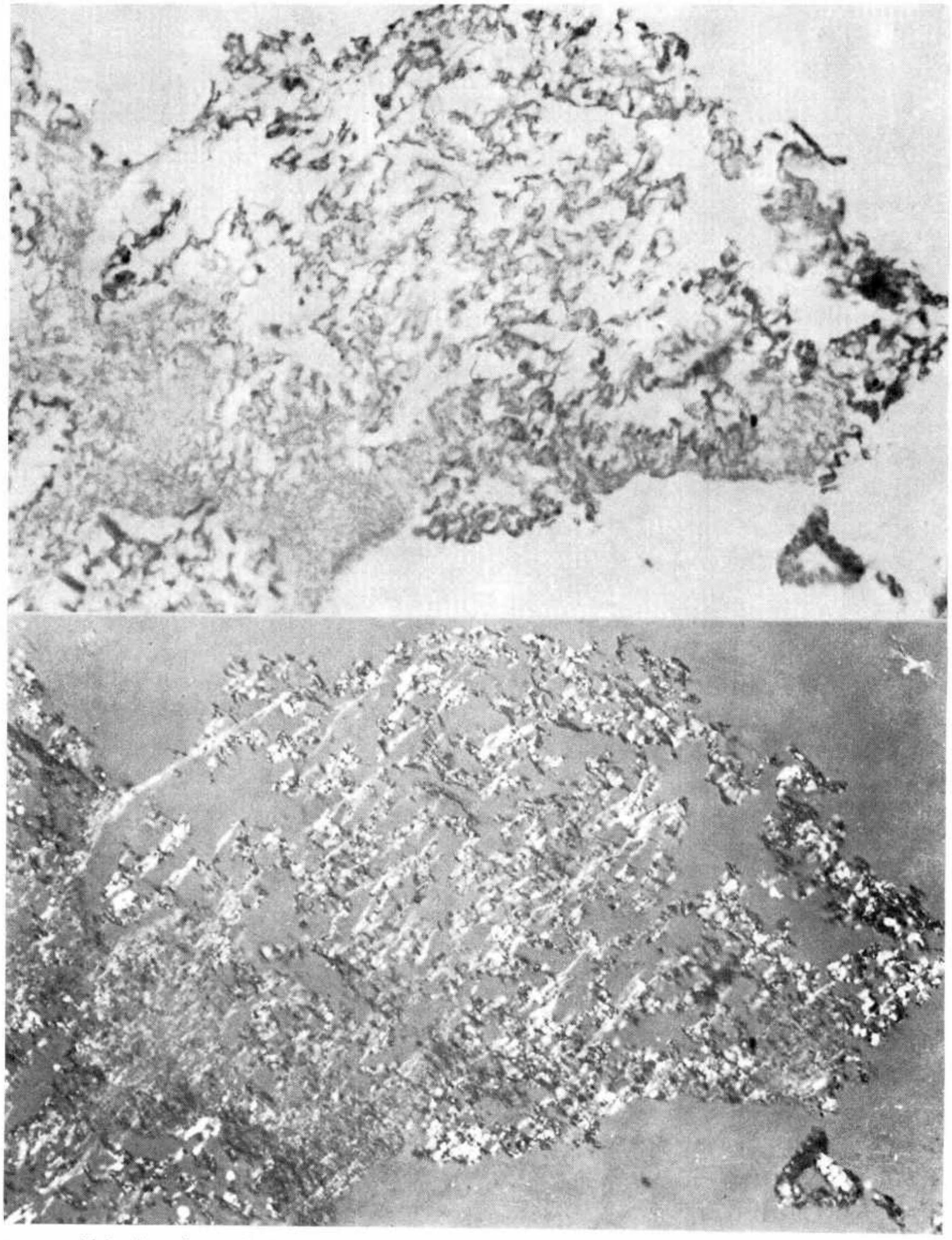


FIG. 10 *Light photomicrograph of vitreous smear stained with congo red*; (a, top) *viewed by ordinary light and* (b, bottom) *viewed by polarized light which reveals green dichroism and birefringent nature of the material.* × 200

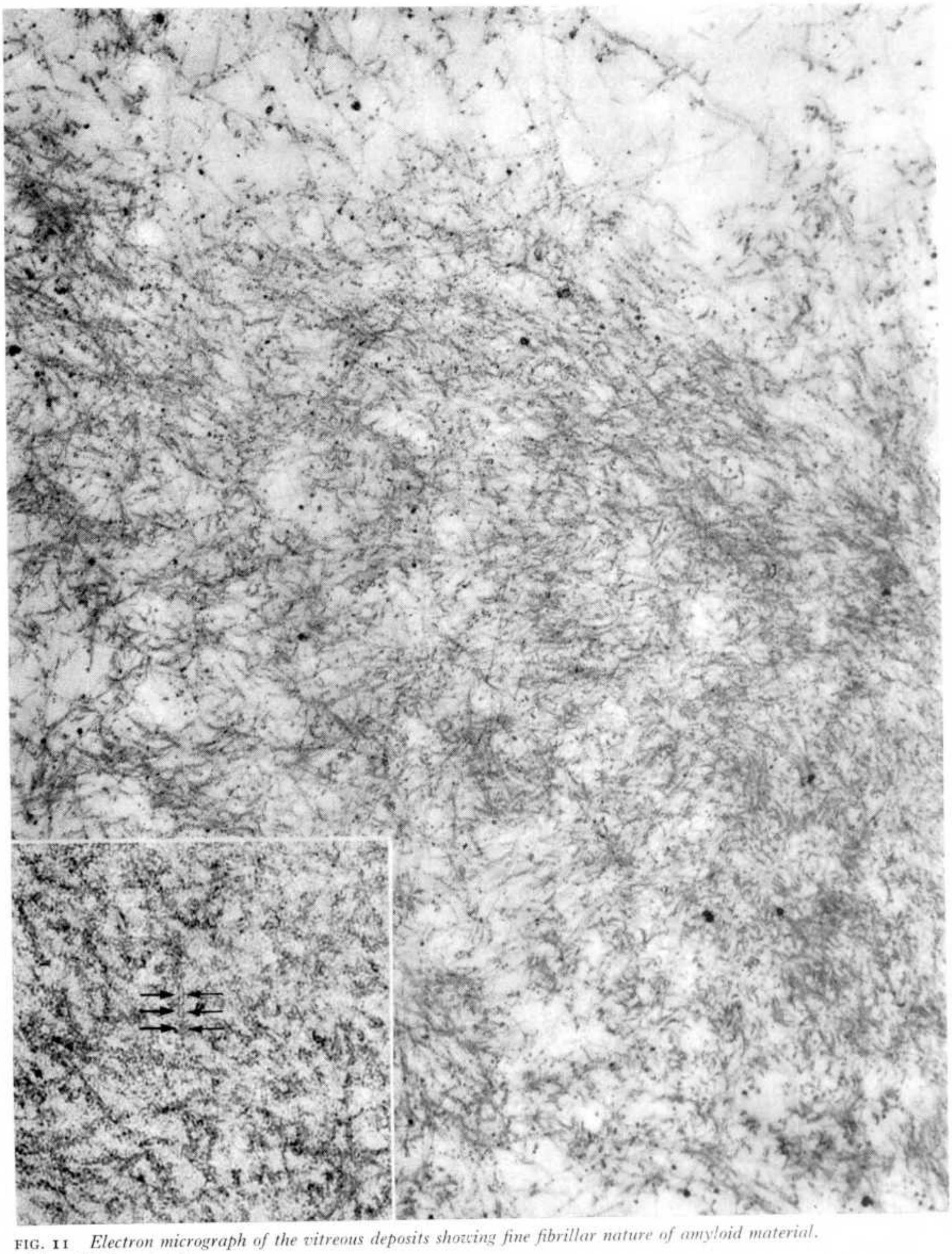


FIG. 11 *Electron micrograph of the vitreous deposits showing fine fibrillar nature of amyloid material. UA and LC* × 50 000.

Inset: *Amyloid fibrils at higher magnification. Individual fibrils have beaded profile and appear to be composed of two laterally-aligned filaments (arrows). UA and LC* × 140 000 discussed in the light of current concepts of amyloidosis. Since the vitreous opacities due to amyloid deposits appear to be one of the manifestations of systemic amyloid disease, surgical removal of the opacities by vitrectomy may not produce long-lasting results. Moreover, in contemplating surgical treatment the ophthalmologist should bear in mind the poor prognosis of systemic amyloidosis.

We thank Mr R. K. Blach for his encouragement and permission to publish details of Cases 1 and 2, Mr Frank Law for permission to publish an account of Case 3, and Mr N. Brown for help in microphotography. Technical assistance was provided by Mrs T. Brittain, Mr R. Alexander, and Mr R. Howes, and secretarial assistance by Miss C. Wilson and Mrs S. Bird. This work was supported in part by the Locally Organized Clinical Research Scheme of Moorfields Eye Hospital.

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Treatment of Behçet's disease with chlorambucil

DIM. TRICOULIS
From the Ophthalmological Department of the Greek Church's General Hospital, Athens, Greece

Behçet's disease is more common and widespread than was previously thought, especially in the Middle East, the Mediterranean countries, and Japan (Abdalla and Bahgat, 1973). Loss of visual acuity is one of the most frequent, as well as the most serious, of its varied manifestations. Total blindness is often inevitable and the rate of deterioration of sight may be used as a criterion for assessing the effectiveness of any treatment (Mamo, 1970).

Various kinds of treatment have been tried, but with disappointing results. Corticosteroid therapy usually gives transient improvement, but does not modify the relentless course of the disease nor its final outcome. Heavy doses of corticosteroids have only a mild delaying effect upon the onset of blindness (Mamo and Azzam, 1970). Interest was therefore aroused by reports of improvement after therapy with immunosuppressive drugs, especially chlorambucil (Abdalla and Bahgat, 1973; Buckley and Gills, 1969; François and Van Oye, 1973; Godfrey, Epstein, O'Connor, Kimura, Hogan, and Nozik, 1974; Mamo and Azzam, 1970; Pezzi, 1972; Rosselet, Saudan, and Zenklusen, 1968; Smulders and Oosterhuis, 1975; Wong, 1969).

Material and methods

Five patients with Behçet's disease were followed-up during a period of 2 years. Each patient showed at least the triad of uveitis, genital and oral lesions. Table I shows the main clinical findings before treatment was started; Table II summarizes their ocular findings. All the patients were receiving systemic steroids and some were also having subconjunctival or retrobulbar injections of 40 mg methylprednisolone (Depot Medrol) and atropine drops locally. In spite of such treatment recurrences of symptoms became more frequent and vision gradually deteriorated.

Three daily doses of chlorambucil (Leukeran) 6 to 8 mg were taken after meals for 3 months and for a further 3 months 6 mg were given on alternate days (Perkins, 1974). In the meantime the corticosteroids were gradually discontinued. The patients were seen weekly for 2 months and then monthly. White blood cell and platelet counts were made weekly. If the total white cell count falls below 3·500/mm^3 or the platelet count below 100·000/mm^3 the drug should be discontinued. In none of our patients was this necessary.

Two of the patients (Cases 1 and 3) had previously been treated with azathioprine for 6 months without any effect.

Results

In all patients there was a remission of the ocular lesions and other manifestations of the disease. This remission started within a few weeks of the addition of chlorambucil to the treatment. In all patients it was possible to reduce gradually and to stop completely the regimen of orally-administered corticosteroids 2 months after starting chlorambucil. The regimen of atropine and corticosteroid drops or injections locally was also discontinued 2 to 3 weeks after starting therapy with chlorambucil.

In all cases the uveitis quietened down and the flare and cells in the anterior chamber disappeared. Remission was obtained in all cases of posterior uveitis and neuroretinitis. The vascular sheathing of the retina remained stationary, and no further ocular damage was recorded. In none of our patients did vision deteriorate even in the two who were followed-up for 2 years. In some the visual acuity improved (Tables III and IV).

In two patients (Cases 1 and 2) there were mild recurrences of posterior uveitis 8 to 10 months after the treatment with chlorambucil had stopped, but the inflammation soon disappeared with a small dose of corticosteroids and another chlorambucil regimen for 3 months. All patients showed a definite improvement of aphthous oral lesions, skin lesions, thrombophlebitis, and other manifestations. There were occasional recurrences of mucocutaneous lesions in some cases, but these were milder and less numerous than before treatment with chlorambucil.

The drug was well tolerated in all patients except one who complained of a mild epigastric burning and fatigue.

Discussion

Cytotoxic drugs are administered in inflammatory disease of uncertain cause because of their immunosuppressive properties. These drugs interrupt nucleic acid and protein synthesis, thereby inhibiting various immune responses at different stages (Steinberg, Plotz, Wolff, Wong, Agus, and Decker, 1972). The chemotherapeutic activity of chloram-

Address for reprints: Dr D. Tricoulis, 55 Skoupha Str, Athens 135, Greece

Table I *Clinical findings*

Case no.	*Sex*	*Age (yr)*	*Duration of disease (mth)*	*Ocular findings*	*Oral ulcers*	*Scrotal lesions*	*Erythema nodosum*	*Thrombo-phlebitis*	*Arthro-pathy*	*CNS involve-ment*
1	Male	41	78	+	+	+	+	+	+	−
2	Male	38	71	+	+	+	+	+	+	+
3	Male	49	82	+	+	+	−	−	−	+
4	Male	29	62	+	+	+	+	−	+	−
5	Male	28	26	+	+	+	−	−	−	−

Table II *Main ocular findings before treatment*

		Iridocyclitis							
Case no.	*Eye*	*With hypopyon*	*Without hypopyon*	*Posterior uveitis*	*Posterior subcapsular cataract*	*Neuro-retinitis*	*Vascular sheathing*	*Retinal haemorrhages*	*Visual-acuity*
1	Right	−	+	+	+	+	+	+	0·1
	Left	−	+	+	−	+	+	+	0·4
2	Right	−	+	+	+	+	+	+	0·2
	Left	−	+	+	−	+	+	+	0·6
3	Right	+	−	+	+	+	+	+	CF
	Left	+	−	+	+	+	+	+	PL
4	Right	+	−	+	+	Fundus not seen			HM
	Left	+	−	+	+				PL
5	Right	−	+	+	−	+	+	+	0·5
	Left	−	+	+	−	+	+	+	0·8

CF = Counting fingers HM = Hand movements PL = Perception of light

bucil is attributed to the formation of electrophilic carbonium ions that alkylate or form covalent linkages with neutrophilic substances. The specific activity of chlorambucil is influenced by the electron-withdrawing capacity of the aromatic ring which reduces the rate of carbonium ion formation. This permits oral administration and distribution to sites of action, before it reacts with neutrophilic substances (Godfrey and others, 1974). Immunosuppressive drugs have been shown to be potentially useful adjuncts in the short-term therapy of ocular inflammation (Wong, 1969). Results of experimental studies with mercaptopurine in allergic uveitis in rabbits (Wirostko and Halbert, 1962) support this clinical finding.

There are several reports on the treatment of corticosteroid-resistant uveal tract inflammations with various immunosuppressive drugs. Clinically favourable results have been reported in some cases using azathioprine, methotrexate, and cyclophosamide but in others no change was observed (Newell, Krill, and Thomson, 1966; Newell and Krill, 1967; Buckley and Gills, 1969; François and Van Oye, 1973; Godfrey and others, 1974; Laatikainen and Erkkida, 1974; Moore, 1968; Rosselet and others, 1968; Wong, 1969).

Favourable reports on chlorambucil in the treatment of Behçet's disease have been published recently (Abdalla and Bahgat, 1973; Godfrey and others, 1974; Mamo and Azzam, 1970; Pezzi, 1972; Smulders and Oosterhuis, 1975).

Our results confirm those of other authors, although the protocol in some studies was different. In our work there was no control group, each patient serving as his own control. The assessment of the effect of the drug was made individually by comparing the course of the disease before and after treatment.

As has been shown (Mamo, 1970), loss of visual acuity occurs on average after 3 to 6 years of onset of ocular symptoms. The steroids have only a mild delaying effect upon the rate of visual loss, so this information acts as a base line in the assessment of a new treatment.

All patients who were treated with chlorambucil in our study improved. They all had a long-lasting remission without serious toxic reactions or side-effects of the drug. Two patients suffered benign relapses of posterior uveitis 8 to 10 months after the treatment had been stopped.

In Behçet's disease the damage to the ocular tissues and especially to the retina is essentially

Table III *Effect of treatment with chlorambucil and corticosteroids*

Type of eye lesion	*No. of cases*	*Remission*	*Partial improvement*	*No change*	*Deterioration*
Iridocyclitis	5	3	2	0	0
Posterior uveitis	5	3	2	0	0
Neuroretinitis	4	2	2	0	0
Retinal vasculitis	4	0	0	4	0

Table IV *Effect of treatment upon visual acuity*

Case no.	*Eye*	*Visual acuity*		*Duration of treatment (mth)*
		Before treatment	*During treatment*	
1	Right	0·1	0·1	24
	Left	0·4	0·6	
2	Right	0·2	0·2	23
	Left	0·6	0·6	
3	Right	CF	0·1	18
	Left	PL	PL	
4	Right	HM	HM	14
	Left	PL	PL	
5	Right	0·5	0·8	10
	Left	0·8	1·0	

CF = Counting fingers HM = Hand movements PL = Perception of light

irreversible, so that a complete cure is impossible. The utmost that can be hoped for is arrest of the disease. Thus far, it seems that this goal may have been attained, although a much longer follow-up period is needed.

Summary

Five patients with Behçet's disease in the active and progressive stages were treated with chlorambucil (Leukeran). In all patients a long-lasting remission was obtained, the ocular lesions did not progress and the vision did not deteriorate. Follow-up varied between 10 and 24 months. Results were encouraging and the form of treatment with chlorambucil and small doses of corticosteroids was superior to other forms of therapy.

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Optic neuritis in the Landry–Guillain-Barré–Strohl syndrome

PETER O. BEHAN, SIMMONS LESSELL, AND MARTIN ROCHE
From the Department of Neurology and Ophthalmology, Boston University, School of Medicine and the Institute of Neurological Sciences, Glasgow

The Landry–Guillain-Barré–Strohl (LG–BS) syndrome is presumed to be due to cell-mediated autohypersensitivity to peripheral nerve myelin (Asbury, Arnason, and Adams, 1969; Behan, Behan, Feldman, and Kies, 1972). Optic neuritis, which is a rare complication, would indicate involvement of central nervous system myelin. This is a report of a patient with the LG–BS syndrome and bilateral optic neuritis whose immunological status we investigated.

Case report

A 17-year-old girl was admitted to hospital because of arm and leg weakness. She had had a cough, malaise, and fever 2 weeks earlier. Five days before her illness she had experienced a 'pins and needles' sensation in her hands and feet, and had felt generally weak. Within a few days she neither could walk nor use her hands, and her face felt tired. Her history included congenital scoliosis and the illicit use of a variety of drugs (both intravenously and by mouth); her past neurological history was negative. On admission to hospital she was alert, co-operative, and intelligent and her vital signs were normal. Her best correctable visual acuity was 20/25 in each eye and the fundi were normal. There was bilateral weakness of the facial musculature and of the flexor muscles of the neck. She was quadriparetic and areflexic but the sensation was not impaired. The only laboratory finding on admission that was abnormal was a cerebrospinal fluid protein of 267 mg/100 ml. The fluid was clear, contained no cells, and was under normal pressure.

Within 10 days she became quadriplegic and developed impairment of respiration, but no artificial assistance of respiration became necessary. Two weeks after admission she complained of blurring of vision of both eyes. Three weeks after admission she complained that her vision had become worse and that there was pain in her eyes on movement. Her visual acuity was then found to be 20/70 in each eye with dyschromatopsia. The pupils responded subnormally to light stimulation but normally to attempts at near vision. She had a central scotoma to the 1 mm white object on the 2 m tangent screen in each eye. Both optic discs were swollen and there were papillary and peripapillary haemorrhages. Fluorescein angiography showed leakage of dye from the tissues of the optic nerve heads in both eyes. The cerebrospinal fluid at that time had a normal pressure and contained no cells, but the protein content was 300 mg/100 ml. She was treated with prednisone which gave immediate relief of pain but did not improve the visual acuity. After 9 days the prednisone was discontinued and the visual acuity gradually improved during the next 3 months. Ultimately a visual acuity of 20/25 was recorded in both eyes with normal colour vision, visual fields, and fundi. She made an excellent recovery from her polyneuritis.

Immunological studies

No abnormalities were found in the levels of any of the major immunoglobulins determined on three occasions throughout the patient's stay in hospital.

Complement-fixing antibodies were determined (Melnick, 1963) using saline extracts of human whole brain tissue, finely ground human sciatic nerve, and purified human myelin encephalitogenic protein as antigens. A weak titre of 1:8 was found during the second week of her illness to all three antigens. Similarly, precipitating antibody to the same antigens (seen as faint lines) were detected during this time by Ochterlony diffusion technique.

Evidence for cell-mediated immunity to these antigens was obtained by the *in vitro* technique of macrophage migration (Rocklin, Meyers, and David, 1970). In this test mumps and streptokinase/streptodornase antigens were used as controls. The patient had exhibited cutaneous sensitivity to these proteins. Additional control antigens were purified protein derivative (PPD) (the patient was PPD negative) and calf thymus histone. Positive inhibition was found to peripheral nerve tissue extract (35 per cent), central nervous tissue extract (29 per cent), myelin basic protein (27 per cent), streptokinase/streptodornase (40 per cent), and mumps (49 per cent). No inhibition was found with PPD, calf histone, or from cultures without antigen. Delayed hypersensitivity measured *in vivo* thus showed good correlation with that measured *in vitro*.

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Address for reprints: Dr P. O. Behan, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland

Discussion

There can be little doubt that the patient had LG–BS polyneuritis. Her polyneuritis followed a febrile, upper respiratory tract illness and began with lower limb paraesthesia and weakness. There was progression of the weakness with sensory sparing and the total cerebrospinal fluid protein was markedly raised without an increase in the number of cells. The ocular symptoms and signs point to a diagnosis of optic neuritis; blurred vision, pain on eye movement, central scotomas, and dyschromatopsia are characteristic of optic neuritis. Disc swelling (and the abnormalities demonstrated on fluorescein angiography) is compatible with both optic neuritis and papilloedema. Optic neuritis has been described previously in the LG–BS syndrome (Brock and Davidson, 1947; Martin, 1961; Kyrieleis, 1931) but considering the prevalence of the LG–BS syndrome, it must be a rare complication. Papilloedema, however, has frequently been observed. It is generally not accompanied by any visual symptoms, and the visual acuity is usually normal. In the past, instances of optic neuritis have possibly been confused with papilloedema because of the similarities in the fundus. The mechanism of papilloedema in the LG–BS syndrome is uncertain (Morley and Reynolds, 1966). It may reflect brain swelling (Joynt, 1958) or a rise in the cerebrospinal fluid pressure due to blockage of the arachnoidal villi by protein (Denny-Brown, 1952). Hypercapnia and acidosis caused by respiratory insufficiency may also be factors. The mechanism responsible for the optic neuritis is uncertain, but it could represent autoimmune inflammation of the white matter of the optic nerve. The immunological studies in our patient suggest hypersensitivity to both central and peripheral myelin, and humoral antibody in both central and peripheral nervous tissue antigens has previously been demonstrated in over 50 per cent of cases of the LG–BS syndrome (Melnick, 1963).

It is known that the antigen which causes experimental allergic encephalomyelitis (EAE) is present in peripheral nerve (Abramsky, Teitelbaum, Webb, and Arnon, 1975). Animals immunized with whole peripheral nerve tissue develop lesions of the central nervous system (Waksman, 1963). The possible causative antigens in experimental allergic neuritis (EAN)—an animal model for LG–BS polyneuritis—produced both EAE and EAN when injected into animals (Abramsky and others, 1975). The reason advanced for this finding is that the antigen responsible for EAN contains active sites for both EAN and EAE induction, but that the site for EAE is normally blocked by the conformation of the protein in the normal myelin substructure (Brostoff, Burnett, Lampert, and Eylar, 1972). Sensitivity to central myelin in our patient may thus have resulted from the liberation of sequestered central nervous system myelin from the initial lesions in the peripheral nerve.

Summary

A patient with typical Landry–Guillain-Barré–Strohl syndrome (LG–BS) developed bilateral optic neuritis. Laboratory studies showed hypersensitivity to both central and peripheral nervous tissue myelin. The occurrence of optic neuritis is presumably due to autohypersensitivity to central nervous tissue myelin. The initial lesions of the LG–BS syndrome in the peripheral nerves might have liberated sequestered antigens that cross-reacted with central nervous system myelin.

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Uhthoff's syndrome

G. D. PERKIN* AND F. CLIFFORD ROSE
From the Medical Ophthalmology Unit, St Thomas's Hospital, London

Uhthoff (1890), in a survey of the ophthalmological features of 100 patients with multiple sclerosis, described four who had blurring of vision during exercise. Subsequent reports have confirmed the association and added other precipitating factors. As part of a follow-up study of patients with optic neuritis (Rose, Friedmann, Bowden, and Perkin, 1972), the prevalence of this syndrome was ascertained and an attempt made to correlate its occurrence with various parameters of optic nerve function.

Methods

Altogether 125 patients admitted to the Medical Ophthalmology Unit of the Royal Eye Hospital with a diagnosis of optic neuritis were reviewed. The criteria for the diagnosis were those given by Rose (1972). Those with a history of visual symptoms exceeding 1 month were excluded.

During follow-up, patients were specifically asked about transient visual blurring and any precipitating factors. Visual acuities were recorded, colour vision tested, and macular thresholds and visual fields measured using the Friedmann visual field analyser.

In assessing final visual function, figures for visual acuities and macular thresholds have been used only if stable values had been recorded on at least two successive occasions, or, with single measurements of macular threshold, if at least 6 months had elapsed since the original attack.

Some of the patients were being treated with corticosteroids at the time of the initial attack. A separate analysis (Bowden, Bowden, Friedmann, Perkin, and Rose, 1974) showed that this had no effect on the final visual acuity, and these patients have, therefore, been included.

Results

Of the 125 patients, 41 (32·8 per cent) had noted episodes of transient visual blurring after recovery. Table I gives details of the precipitating factors, and shows that 25 patients were affected by one, ten patients by two, four patients by three, and two patients by four factors.

The clinical features at presentation of patients with or without subsequent transient blurring are compared in Table II. The criteria for a diagnosis of multiple sclerosis were those of Rose and others (1972); the differences are not significant.

In Table III, a similar comparison is made at the time of the follow-up examination. Again, the differences are not significant.

Discussion

Although 60 years elapsed between Uhthoff's description and the confirmation by Brickner (1950) of the association between exercise and the deterioration of visual acuity in patients with previous optic neuritis, McAlpine and Compston (1952) subsequently suggested that up to one-third of patients with multiple sclerosis could have symptoms (including visual blurring) induced or worsened by exercise.

There has been no previous attempt to correlate the clinical features of optic neuritis with the subsequent development of transient visual blurring. Although no such correlations were found in this study, the difference between the two groups in the proportion of patients having more than one attack of optic neuritis in the originally affected eye only just fails to reach a level of significance. Among the seven patients with blurring of vision on exercise described by Thomson (1966), three had had two or more attacks of unilateral optic neuritis, as had two of the four patients with the

Table I *Factors producing transient blurring*

	Patients	
Factor	*No.*	*Percentage*
Affective disturbance	20	16
Exercise	14	11
Temperature change	10	8
Menstruation	10	8
Unknown	4	3·2
Increased illumination	4	3·2
Eating	2	1·6
Smoking	1	0·8

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*At present Senior Registrar, The National Hospitals for Nervous Diseases (Maida Vale Hospital) and University College Hospital

Address for reprints: G. D. Perkin, Maida Vale Hospital, Maida Vale, London W9

Table II *Clinical features of 125 patients at presentation*

Features at presentation	*With subsequent transient blurring*	*Without subsequent transient blurring*
No. of patients	41	84
Percentage of females	65·9	64·3
Age at presentation (mean) (years)	33·2	34·9
Eye affected (including multiple attacks)	Right 28	Right 51
	Left 28	Left 50
Smokers (per cent)	65·9	54·3
20 cigarettes or more/day	24·4	24·4
Evidence of multiple sclerosis at onset (all criteria) (per cent)	53·7	39·5
Percentage* with visual acuity of 6/36 or better at onset	27·6	42·2
Duration of symptoms before admission (mean) (days)	15·2	16·0

*Excluding patients with previous attacks of optic neuritis in the same eye

Table III *Clinical features of 125 patients at follow-up*

Features at follow-up		*With transient blurring*	*Without transient blurring*
Attacks of optic neuritis (per cent)	Single episode	75·6	87·5*
	More than 1	24·4	12·5*
	in originally affected eye	17·1	5*
	More than 2	9·8	2·5*
	Multiple (L= left, R= right)	LL LL LL LR LR LR LLR RRL RRR LLRR	LL RR LR LR LR LR LR LR RRRL RRRRRLL
Evidence of multiple sclerosis at follow-up (all criteria) (per cent)		87·8	78·5
Mean follow-up for assessment of dissemination (months)		30·9	34·0
Percentage reaching visual acuity of 6/6†		77·4	75
Final macular threshold†		2·31	2·23
Time to measurement of stable macular threshold (weeks)		18	11
Colour vision: red/green abnormalities ± other defects† (per cent)		64·5 (unilateral 90)	44·4 (unilateral 81)
Percentage treated with steroids at onset		9·8	14·8

*These percentages were calculated on 80 patients. The possibility of multiple attacks had not been ascertained in the remaining four
†Excluding patients with multiple attacks of optic neuritis in the same eye

same symptom reported by Goldstein and Cogan (1964).

There are no other published series of the prevalence of transient visual blurring after optic neuritis with which to compare the figure of 32·8 per cent obtained in this study. McAlpine and Compston (1952), however, described in patients with established multiple sclerosis a short-lived deterioration of any symptom with exercise in 34·7 per cent, with emotional stimuli in 33 per cent, and with heat in 13·5 per cent.

The exacerbation of visual and other symptoms by increased temperature was probably first recorded by Young and Bennett (1927) in patients treated with typhoid vaccine therapy. Lindemulder (1930) and Collins (1938) observed similar effects in patients treated with hot baths. Subjective worsening of symptoms by heat occurred in up to 62 per cent of the patients with multiple sclerosis interviewed by Simons (1937). The phenomenon has since been recorded by many authors (Franklin and Brickner, 1947; Brickner, 1950; Guthrie, 1951; McAlpine and Compston, 1952; Edmund and Fog, 1955; McDowell, Jeffreys, and Nelson, 1958; Nelson and McDowell, 1959; Earl, 1964; Goldstein and Cogan, 1964; Thomson, 1966; Namerow, 1968). Although cooling generally has the opposite effect, deterioration has been reported (Simons, 1937; McAlpine and Compston, 1952). The frequency with which hot baths produce symptomatic exacerbations becomes more striking when it is recalled that hot baths also produce over-breathing with hypocapnia (Hill and Flack, 1909) which is now known to cause improvement in certain manifestations of the disease—for example, scotoma size (Davis, Becker, Michael, and Sorensen, 1970).

Pratt (1951) showed that a significantly higher proportion of patients with multiple sclerosis had symptoms exacerbated by certain emotional stimuli, than controls with other diseases of the nervous system. During menstruation patients usually improve symptomatically (McAlpine and Compston, 1952), although McFarland (1969) described one case with pronounced exacerbations.

Smoking was first implicated as a factor by Franklin and Brickner (1947). Its transient adverse effect on vision was noted by Brickner (1950) and on other symptoms by Courville, Maschmeyer, and Delay (1964). In view of the adverse effect of smoking on visual acuity in other situations, a separate assessment of residual optic nerve function was made, according to the smoking habits at the time of the original attack. Apart from a just significantly ($P < 0\cdot05$) higher incidence of colour vision defects in those smoking 20 or more cigarettes a day compared with non-smokers, no influence was detected (Perkin, Bowden, and Rose, 1975).

Although the symptom of transient visual blurring with certain stimuli seems to be particularly associated with multiple sclerosis, it is probably not confined to this disease. McDowell and others (1958) described four patients with other disorders of the central nervous system who developed visual blurring on immersion in a hot bath.

The pathogenesis of these phenomena is uncertain. Most patients in this series were affected by a single factor, and it seems unlikely that such diverse precipitants as heat, smoking, and eating could all operate by the same mechanism. It has been suggested that a critical reduction in blood flow in the region of the plaques induced by cutaneous, muscular, or splanchnic vasodilatation explains the effect of heat, exercise, or eating. With the experimental evidence that increasing temperature can cause conduction block in demyelinated nerve fibres (Davis and Jacobson, 1971), an alternative mechanism for the effect of heating, and possibly exercise, has appeared. Thus, in one patient investigated by Namerow (1968), exercise produced a deterioration in visual acuity only when accompanied by a rise in body temperature, although a similar case described by Goldstein and Cogan (1964) maintained a stable temperature during exercise, despite a deterioration in vision.

Rasminsky (1973) showed that a rise in temperature by as little as 0·5°C can cause reversible conduction block in single demyelinated peripheral nerve fibres. The blocking effect, however, involves only the most severely demyelinated internodes, those less affected actually showing a reduced conduction time. Rasminsky suggested, on the basis of these findings, that patients with multiple sclerosis who develop symptoms with a slight increase in body temperature must have many fibres with severely demyelinated internodes. He concludes that the overall conduction velocity of such fibres would be significantly reduced.

Although the extent of the delay in latencies of the visually-evoked responses found in some patients with multiple sclerosis probably cannot be explained solely on the basis of slowing of conduction in demyelinated fibres (McDonald, 1974; Heron, Regan, and Milner, 1974; Asselman, Chadwick, and Marsden, 1975), if this slowing remains an important factor in their development, certain predictions are possible.

First, the incidence of transient visual blurring in relation to heating should be maximal in those patients with the longest latencies. Secondly, observation of the responses in patients who undergo heating would be expected to show a reduction in amplitude of the response (due to conduction block in many of the fibres contributing to it) with possibly a shortening in latency (because of enhanced conduction in the unblocked fibres).

In considering the pathogenesis of the Uhthoff phenomenon in conditions other than multiple sclerosis, it may well be significant that two of the three patients described (McDowell and others, 1958) in whom a diagnosis had been made had conditions (pituitary tumour with suprasellar extension, and Friedreich's ataxia) that were capable of causing prolonged latencies in visually-evoked responses.

Summary

A total of 125 patients with a previous episode of optic neuritis was followed to assess the subsequent prevalence of transient visual blurring. 32·8 per cent developed this symptom and the precipitating factors were identified. No correlations were found between the development of the symptom and the parameters of optic nerve function studied.

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A clinical approach to the aetiology of uveitis in Bantu adults

JEFFREY FREEDMAN
From the University of Witwatersrand, St John's Eye Hospital Baragwanath, Johannesburg, South Africa, and State University of New York, USA

Duke-Elder (1966) stated that, although numerous authors have published figures showing the incidence of different aetiological factors in uveitis, it is still difficult to obtain figures of an overall distribution because many papers deal with only one type of uveitis. Although a few clinical pictures can be recognized with some certainty, the aetiology of most cases of uveitis have persistently proved elusive. The results obtained after investigations into the aetiology of uveitis in adult Bantus in South Africa during a 2-year period are presented.

Clinical study

During a 2-year-period 311 adult Bantus were seen; their sexes and ages are shown in Table I. The investigations of possible aetiological factors were divided into two main groups. In the first group all patients were examined by a predetermined set of laboratory and clinical studies. These comprised:

1. Radiological examination of chest, teeth, sinuses, and lumbo-sacral joints.
2. Blood tests including a full blood count, erythrocyte sedimentation rate (ESR), antistreptolysin titre, mucoprotein levels, blood sugar levels, gonococcal complement-fixation test, toxoplasma dye and complement-fixation tests, Rose latex test for arthritis, serum protein electrophoresis, histoplasma complement-fixation test, and Wassermann, *Treponema pallidum* immobilization, and fluorescein antibody tests for syphilis. Stools and urine were examined for parasites and micro-organisms, and there were skin tests for tuberculosis.

A second group of investigations based on the identification of specific clinical entities was also carried out. Here a presumptive aetiological diagnosis was made on clinical examination of the patients and confirmed by the appropriate special investigations where these existed.

The specific clinical entities seen in this study included: tuberculosis, sarcoidosis, sympathetic ophthalmitis, leprosy, syphilis, Vogt-Koyanagi-Harada syndrome, intraocular parasites, toxoplasmosis, and presumed histoplasmosis syndrome.

Group 1 (159 patients)

In these patients there was no obvious clinical cause for the uveitis. Results of special investigations were as follows:

1. The full blood count results were non-contributory as regards significant abnormalities.
2. Altogether 27 patients had a Westergren ESR of 23 mm/1st hour or greater (Table II). The highest ESR recorded was 69. Of the 159 patients 16 per cent had a raised ESR.
3. Gamma globulins were raised in 11 patients (8 per cent).
4. The Rose latex test for rheumatoid arthritis was positive in three patients none of whom had any clinical evidence of rheumatic disease.
5. The gonococcal complement-fixation test was positive in five patients none of whom had a urethral discharge concurrent with the uveitis.
6. The Wassermann reaction for syphilis was positive in 20 patients.
7. The toxoplasmosis dye test was positive in 11 patients.
8. The histoplasmosis complement-fixation test was positive in two patients, one of whom had fundus lesions suggestive of the disease.
9. Urine analysis and stool investigation did not reveal any parasites.
10. Radiological investigations revealed three patients with active sinusitis.

Table I *Age and sex distribution of Bantus with uveitis*

Age (years)	*Males*	*Females*
0–14	14	27
15–24	35	20
25–44	88	80
45–64	44	37
65+	4	6
Total	185	170

Address for reprints: J. Freedman, MD, State University of New York, Downstate Medical Center, Department of Surgery, Division of Ophthalmology, 450 Clarkson Avenue, Brooklyn, New York 11203, USA

Table II *Number and percentage of uveitis patients with positive results for routine serological and radiological investigations*

Test	*Total*	*Per cent*
X-ray sinus	3	2
ESR	27	16
Mucoprotein	13	9
Alpha globulin	11	8
Antistreptolysin titre	9	5·5
Rose latex	3	2
Gonococcal complement-fixation	5	3·2
Venereal Disease Reference Laboratory	20	12
Toxoplasma dye and complement-fixation	11	7
Histoplasma complement-fixation	2	1

11. Nine patients had an elevated antistreptolysin titre. These findings are summarized in Table II.

Group 2

This dealt with the following clinical entities in uveitis:

Vogt-Koyanagi-Harada syndrome

Two cases of this syndrome were seen, in two women aged 32 and 36 years, but neither presented with the full-blown clinical syndrome. The first patient presented with severe bilateral anterior uveitis characterized by intense scarring with extensive posterior synechiae, kerato-uveitis, and cataract formation. Depigmentation of the skin around the eyes with poliosis was present. No deafness or central nervous system involvement was noted. Although some scarring in terms of posterior synechiae occurred in both eyes, the visual acuity remained 20/20 in both eyes. A third case which had features of Vogt-Koyanagi-Harada syndrome was diagnosed presumptively as sympathetic ophthalmitis. A history of a penetrating injury to the left eye was given. The injured eye was not sutured and was removed 1 month later. Two weeks after injury the right eye became painful and developed a severe anterior uveitis with a final visual acuity of hand movements at 1 m. One month after the injury depigmentation of the skin of the face, legs, and hands occurred. No other features suggestive of Vogt-Koyanagi-Harada syndrome such as deafness or central nervous system involvement was noted. The diagnosis might have been Vogt-Koyanagi-Harada syndrome or sympathetic ophthalmitis, the sequence of events suggesting the latter, but confirmation was denied as no histology of the enucleated eye was available. This case illustrates the clinical similiarity between sympathetic ophthalmitis and Vogt-Koyanagi-Harada syndrome. In all three cases described scarring of the eyes occurred, and in two out of the three, the final visual acuity was poor.

Leprosy

Four cases of leprosy were seen, two in men and two in women. The two men presented with the tuberculoid type, each having bilateral facial nerve palsies, exposure keratitis, and secondary uveitis; one also had a hypopyon ulcer. The two women both presented with mixed form of leprosy—lepromatous and tuberculous. They both had primary anterior uveitis without associated seventh nerve palsies. In these two cases, scarring of the anterior segment was severe.

Tuberculosis

Two men presenting with uveitis were diagnosed as having tuberculous uveitis. The first patient presented with bilateral anterior uveitis. The left eye had no perception of light and optic atrophy and the right eye had papilloedema with diffuse active chorio-retinitis. The chest x ray revealed active tuberculosis. The uveitis responded well with a combination of steroid and anti-tuberculosis therapy. The second patient was a 35-year-old man who presented with bilateral anterior uveitis with a right-sided proptosis. Once again a chest x ray revealed active tuberculosis. In both these cases the clinical entity of uveitis due to tuberculosis was diagnosed because of the association of uveitis with active tuberculosis and this was further substantiated in the first case by what looked like a possible tuberculous chorio-retinitis.

Sarcoidosis

Two proved cases of sarcoidosis were seen. The first, a woman aged 38 years, presented with bilateral anterior granulomatous uveitis. She developed diffuse posterior synechiae in both eyes, the fundus being normal. The second case, a man aged 30 years, presented with bilateral granulomatous uveitis with inferior vitreous opacities. After treatment with systemic and local steroids both patients had a final visual acuity of 20/20 in both eyes. In addition both patients had positive Kveim tests. Diagnosis in the woman was further substantiated by positive histology after scalene node biopsy. She suffered recurrent attacks of uveitis over a 1-year-period and the man had a single recurrence in a follow-up of 1 year.

Syphilis

The diagnosis of syphilitic uveitis was based on a clinical appearance suggestive of the disease, associated with positive serology. Spirochaetes were not detected in the aqueous tested and no cases having positive serology but without typical clinical features are included. Altogether four presumptive syphilitic uveitis cases were seen, two being in men and two in women. The first man aged 19 years presented with bilateral vitreous haemorrhages and bilateral anterior uveitis. A strongly positive *Treponema pallidum* immobilization (TPI) test was present and no blood dyscrasia was noted. Marked improvement of the vitreous haemorrhages occurred with antibiotic therapy and systemic steroids. The second man presented with bilateral anterior uveitis with a left-sided hyphaema and associated fundal haemorrhages; a strongly positive Wassermann test was present. The first woman presented with a large inferior ciliary staphyloma and a lens dislocated into the vitreous in the right eye. The vitreous contained many cells as did the anterior chamber. The left eye had an anterior and posterior uveitis with an exudative detachment. There was no history of trauma and the TPI test, but not the Venereal Disease Reference Laboratory (VDRL) test, was positive. Thus, long-standing syphilis was diagnosed. The second woman presented with bilateral diffuse uveitis with exudative lesions of the choroid, as well as old areas of chorioretinitis. Again the TPI test was positive and the VDRL test negative, suggesting long-standing syphilis.

Parasitic infections

One patient, a 45-year-old man, presented with a uveitis and associated parasitic infestation. The right eye had an anterior uveitis with cells in the vitreous as well. Within the vitreous a large, live cysticercus was found associated with a hole at the macula. The diagnosis was made by direct observation of the parasite; no ova were obtainable from the patient's stools.

Ankylosing spondylitis

Two patients with ankylosing spondylitis and uveitis were seen. The first, a 27-year-old man, presented with a left-sided nongranulomatous uveitis. Both patients had typical clinical and *x* ray features of ankylosing spondylitis.

Toxoplasmosis

Only one case with a typical fundus lesion and positive serology for toxoplasmosis was seen.

Septicaemic retinitis

A 35-year-old woman who had undergone renal transplants developed a perinephric abscess. Associated with this she developed a septicaemic retinitis and associated anterior uveitis.

No cases of chronic cyclitis were seen in the adult patients.

Discussion

In the 159 patients examined fully by clinical and laboratory investigations the significance of the results of the nonspecific tests was as follows:

ESR

This was found to be positive in 16 per cent of patients tested. Norn (1969) found the ESR to be raised in 52 per cent of his cases of uveitis. Leira (1965) found less marked but analogous percentages. The raised ESR indicates general illness such as arthritis or severe forms of uveitis and recrudescences. It seems that, in the absence of arthritis, in cases studied in the Bantu, the raised ESR was due to a severe form of uveitis, which was confirmed clinically. In those cases in which the ESR was raised it was significantly high. It is said to be a bad prognostic sign if the ESR is very high (Norn, 1969) and this certainly seemed to be so in the Bantus; in most of those with a raised ESR, the attacks of uveitis had been severe with the subsequent detrimental sequelae. Thus the ESR may be of prognostic rather than of specific aetiological value.

Serum electrophoresis

In this study, where abnormalities in serum proteins existed (7 per cent of cases), the common abnormality was a rise in the gamma globulins. These findings agree with those of Haut and Campinchi (1973) but the percentages are much lower in the Bantu. A rise in alpha-globulins as noted by Sokolovsky (quoted by Dieckhues and Böke, 1963) and alpha-2-globulins (Aronson, 1968) was not found in the Bantus. The abnormalities noted in the serum proteins are probably only an indication of the reaction of the individual to the uveitis as stated by Aronson (1968) and probably of no aetiological significance. No specific aetiological agent was noted in any case with raised gamma globulins in this study. The Wassermann reaction for syphilis was positive in 12 per cent of cases of uveitis on routine study. In none of these cases was any improvement noted with specific therapy nor was the uveitis typical of that caused by syphilis and the positive Wassermann reaction was probably a coincidental finding. This is again suggested by the fact that 20 per cent of the Bantu population have a positive Wassermann reaction. Therefore, the Wassermann test played an insignificant role in assisting to elucidate an aetiological factor in the patients undergoing routine investigations for uveitis.

The latex test for rheumatoid factor was positive in 2 per cent of the Bantu patients. However, none of these patients manifested any clinical evidence of arthritis and on routine investigation this was not a helpful diagnostic procedure.

Serology for gonorrhoea was positive in 3·2 per cent of the cases studied. This figure is similar to the percentage found by Norn (1969) in his series. However, the uveitis seen in the patients of this study were not typical of gonococcal-induced uveitis and no real improvement occurred with specific therapy. The positive gonococcal serology was not assessed to mean that the uveitis was due to gonococcal organisms.

Routine investigation for toxoplasmosis was tested by two methods, the Sabin-Feldman dye test and the complement-fixation test. The positive results were obtained in 7 per cent of patients on routine testing. However, in none of those was there a rising titre on re-testing, nor was the titre higher than 1:128. Of the 11 patients with positive tests for toxoplasmosis, six had anterior uveitis with no associated fundus lesion, the uveitis probably not being due to *Toxoplasma gondii*. The remaining five patients had fundus lesions only one of which resembled that due to toxoplasmosis. Once again for routine investigation, the toxoplasma serological tests were of no help in the diagnosis of aetiological agents in cases of anterior uveitis.

On routine investigation the histoplasma complement-fixation test was positive in two patients, one of whom had a fundus lesion which was not typical of histoplasmosis and on repeat testing a positive histoplasma result was not obtainable. Histoplasmosis appears not to be a common cause of uveitis in Bantus of South Africa.

Thus in an overall general investigation of 159 adult patients with uveitis, the gleaning in terms of aetiological agents was small.

CLINICAL ENTITIES

Of the two cases diagnosed as Vogt-Koyanagi syndrome, one patient presented with the uveitis first and then the vitiligo, while the second presented with uveitis and vitiligo simultaneously. Both these presentations are acceptable for the diagnosis of Vogt-Koyanagi syndrome. In its classical form the uveitis precedes the vitiligo by 3 weeks to 3 months. Both patients were in their twenties which is the classically described age group. The presentation of diffuse bilateral uveitis is also typical of the disease, as is the poor visual result and scarring as seen in one of the patients. No deafness or central nervous system involvement occurred in either patient but these manifestations occur in only 50 per cent of patients with the disease. It is not surprising that the condition was seen in two Bantus as it obviously predominates in the Far East, Latin America, and the Mediterranean basin, and is therefore an affliction of the heavily pigmented races—yellow and black. The first description in the Bantu was that of Trope and Coetzee (1961). Bruno and McPherson (1949) described the condition in the North American Negro. Surgical intervention, such as lens extraction, does not always give a good result and the prognosis should be guarded. The poor result obtained after lens extraction in one of the Bantu patients certainly followed this dictum. The close interrelationship between sympathetic ophthalmitis and Vogt-Koyanagi-Harada syndrome has been shown clinically in the Bantu first by Trope and Coetzee (1961) and possibly in the case described in this study. This clinical association has been further substantiated on an immunological level by the experiments of Wong, Anderson, and O'Brien (1971), and Hammer (1971), wherein they demonstrated positive lymphocyte transformation in the two conditions suggesting an immunological basis for them. Thus typical forms of Vogt-Koyanagi-Harada syndrome do occur in the Bantus of South Africa.

The incidence of tuberculosis as a possible cause for uveitis was less than 1 per cent in this study. In the Indiana Survey (Schlaegel, 1968) the incidence was 1 per cent and Haut (1966) found it to be 1·8 per cent in his survey. For Cross (1960) tuberculosis represented 14·6 per cent of chronic or recurrent uveitis, while Remky (1960) listed 10 per cent of cases of uveitis due to tuberculosis. There tends to be a balance between the severity of the tuberculosis in the lungs and the uvea. Woods (1973) rarely found active pulmonary tuberculosis in the course of uveal tuberculosis. This would have appeared to be the findings in the two Bantu patients described, in that, although many findings were diagnostic of tuberculosis no bacilli were found in the sputum during the manifestation of the uveitis. The diagnosis of tuberculous uveitis in these two cases remains presumptive as Koch's postulates were not fulfilled. However, the feature brought out by the findings in this study is the now accepted one of a low to non-existent incidence of tuberculous uveitis, particularly in the Bantus.

The two cases of sarcoidosis seen in this study represent an incidence of less than 1 per cent. Sarcoid is said to be an aetiological factor in approximately 3 per cent of cases of uveitis (Woods, 1973). The incidence in the Bantu is unlike that in the American Negro who appears to be abnormally susceptible to the disease. Although sarcoid uveitis is rare in the Bantu, the nature of the uveitis when it does occur is typical of sarcoid uveitis in other racial groups. The incidence of sarcoid in the Bantu is similar to that in the Caucasoid group (0·5 per cent; Haut, 1966), and unlike the frequency of sarcoid uveitis as seen in the American Negro.

Presumptive syphilitic uveitis diagnosed in four patients represents an incidence of 1·3 per cent. Old statistics showed a 25 to 75 per cent incidence and Woods (1973) recognized 4 per cent of uveitis as being due to syphilis. The incidence in Baltimore, USA, as reported by Perkins (1968), was 15·2 per cent. Haut (1966) found an incidence of 1·1 per cent and Witmer (1969) stated that syphilitic uveitis was rare. A number between 1 and 4 per cent probably corresponds to the incidence of syphilitic uveitis. Thus the incidence of possible syphilitic uveitis in the Bantu corresponds to the accepted average and is low when considered against the positive serology in the general Bantu population which is 20 to 25 per cent. The diagnosis in the four Bantu patients remains presumptive as no firm evidence such as locating the spirochaete from the eye was obtained. However, the clinical evidence presented by the four patients indicated that the uveitis was due to syphilis. A hyphaema may be one of the characteristic findings of secondary syphilis. The presence of exudative chorioretinitis is also highly suggestive of syphilis. Uveitis of late syphilis may present with a cataract and ciliary staphyloma probably due to a gumma. Finally, the *Treponema pallidium* immobilization test is negative in normal persons and permits the elimination of false positives. The reaction to the test appears later than other serological reactions and remains positive in a late stage of the disease, being little influenced by therapy. Its positivity in all four cases with the associated clinical uveitis is indicative of the presence of syphilitic uveitis. However, even with the presumptive 1 per cent incidence, syphilis does not seem to be a major aetiological factor in the causation of uveitis in the Bantus of South Africa.

Four cases of leprosy represent 1·3 per cent incidence of leprosy uveitis. The comparison of the incidence of uveitis due to leprosy in other surveys is difficult, as in most surveys the incidence of uveitis in patients with leprosy is not given (Ticho and Bensira, 1970). The two women with mixed leprosy presented with the more severe uveitis as would be expected with lepromatous, or direct involvement uveitis, as compared with the tuberculoid form as seen in the two men. In this study, uveitis was caused by leprosy more often than by sarcoidosis or tuberculosis and presented an easily identifiable clinical entity.

There were only two cases of ankylosing spondylitis associated with uveitis, an incidence of less than 1 per cent. Blagojevic, Parunovic, Nickolick, and Mladenovic (1970) found an incidence in their series of 140 cases of 5 to 20 per cent. Ankylosing spondylitis in association with uveitis is rare in the Bantu and the two cases associated with uveitis are unique.

Only one case with a typical fundus lesion and positive serology for toxoplasmosis was seen. This represents an incidence of 0·3 per cent of uveitis due to toxoplasmosis in the Bantu studied. Van Metre (1968) found an incidence of 14 per cent and Chesterton and Perkins (1967) an incidence of 8 per cent of which 34 per cent were Negroes from the West Indies or West Africa. Hogan, Kimura, and O'Connor (1964), in a study of uveitis in 1584 patients, found 240 patients (15 per cent) with suspected ocular toxoplasmosis; few of these were Negroes. The explanation for this observation was given. The study in Bantus, in which a very low incidence of toxoplasmic uveitis was seen, correlates well with Hogan's observations in American Negroes. On routine testing, a positive serological test for toxoplasmosis was obtained in 7 per cent of the Bantu patients, none of whom had features of ocular toxoplasmosis. This finding of positive serology for toxoplasmosis correlates with the incidence of positive serology for the Bantu population as a whole, which is 10 per cent. From the findings of this study, the nonspecific testing for toxoplasmosis in all cases of uveitis would seem to be unhelpful in elucidating an aetiological factor, and the search for clinical features of toxoplasmosis with subsequent serological testing would seem to be more practical.

Conclusions

The gleanings in terms of an aetiological diagnosis obtained from nonspecific blanket testing of all cases of uveitis would seem to be poor in the Bantus. Where positive aetiological factors were obtained, a clinical diagnosis was more often than not possible, the diagnosis being confirmed by the appropriate special tests. It would seem then, from the findings of this study, that routine investigations of all cases of uveitis along present lines, as advocated by Woods (1961), are usually fruitless, and that the identification of clinical entities, as suggested by Maumenee (1968), is a more logical approach in the investigation of uveitis.

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Brit. J. Ophthal. (1976) **60,** 70

Quantitative tear lysozyme assay in units of activity per microlitre

I. A. MACKIE AND D. V. SEAL
From St George's Hospital and Public Health Laboratory, and Moorfields Eye Hospital, London

Fleming (1922) discovered lysozyme, and in 1932 he assayed the tear level using a dilution technique (Fleming, 1932). He showed that the concentration of lysozyme in tears was up to a thousandfold greater than in serum.

Accurate lysozyme assay has been possible only since the establishment of hen egg lysozyme (HEL) and human lysozyme (HL) standards. Their activity can be accurately measured. HEL standards have recently been used for lysozyme assay in urine, peritoneal fluid, and serum and HL standards have been used for assay in cerebrospinal fluid (Parry, Chandian, and Shahani, 1965; Harrison, Lunt, Scott, and Blainey, 1968; Wardle, 1973; Cacatian, Newman, Josephson, and Tsang, 1974).

Tear fluid is most easily collected by filter paper disc absorption. Results of the total quantity of lysozyme on the discs, have been expressed in diameters of zones of lysis of *Micrococcus lysodeikticus*. Various authors have reported different normal diameters (Bonavida and Sapse, 1968; Bijsterveld, 1969; el Gammel and Salah, 1971; Pietsch, Pearlman, and Durham, 1973; Bijsterveld 1974). Results have also been expressed in µg/µl of uncalibrated HL (Pietsch and others, 1973), of HEL (Covey, Perillie, and Finch, 1971), and calibrated HEL (Osserman and Lawlor, 1966; Friedland, Anderson, and Forster, 1972). Direct comparison of these results is unreliable, because HEL and HL vary in their activity per µg, as shown by the different levels quoted (Harrison and others, 1968; Bonavida and Sapse, 1968; Friedland and others, 1972; Bijsterveld, 1974). In addition, batches of lysozyme standards are prepared by different commercial laboratories; further confusion arises because HL has eight to 12 times the activity of HEL per µg (Osserman and Lawlor, 1966).

In this study, calibrated HEL standards were used in each assay alongside the test discs. The activity of this HEL standard was measured in 'units of activity' per µg, so that direct comparison with other results, in units, could be made. A 'unit of activity' is defined below.

Method

Dried, autoclaved Whatman No. 1 filter paper discs, 6 mm in diameter, were placed inside bijoux bottles which were weighed and put into clear plastic envelopes. The disc was placed in the lower fornix of the conjunctiva with a forceps, allowed to absorb tear fluid, and then replaced in the bottle. Care was taken to avoid collecting the mucus thread in the lower fornix. The bijou bottle, with the wet disc, was reweighed so that the volume of tear fluid could be calculated. Other discs were wetted with standard HEL at a concentration of 1, 3, 5, and 10 µg/µl and the volume absorbed was again estimated by weighing. A control disc of HEL was similarly treated.

Twenty colonies of *M. lysodeikticus*, from a purity plate, were innoculated into 20 ml nutrient broth (Oxoid), and shaken for 2 min. This was flooded on to a 20 cm² plate, containing 250 ml Direct Sensitivity Test Agar (DST-1·2 per cent Oxoid), and dried (Bijsterveld, 1974). The discs for the tests, standards, and controls were placed on the surface of the plate, which was incubated at a temperature of 37°C for 18 h. Zones of lysis of the *M. lysodeikticus* occurred around the discs. The diameters of these zones were measured with precision calipers.

The HEL standard was calibrated in a spectrophotometer by measuring the rate of lysis of a fresh substrate of *M. lysodeikticus* grown for 48 h on Meyer and Hahnel medium (Meyer and Hahnel, 1946; Shugar, 1952). The *M. lysodeikticus* was suspended in M/10 phosphate buffer at pH 7·0. The absorption of the suspension in a 3 ml spectrophotometer cuvette was adjusted to between 0·5 and 0·6 with a wavelength of 450 nm at a temperature of 25°C. Samples of 10, 20, 30, and 40 µl of the 1, 3, 5, and 10 µg/µl HEL standards, each diluted to 0·3 µg/µl, were added to the cuvette so that the concentration of the HEL was known in µg/ml buffer substrate. The decrease in absorption during the first minute was measured.

One 'unit of activity' was defined as that amount of enzyme required to cause a decrease in absorption of the *M. lysodeikticus* substrate, in M/10 phosphate buffer at pH 7·0 and at a temperature 25°C, of 0·001 in the first minute of the reaction, at a wavelength of 450 nm.

The HEL standards had to be kept deep frozen (−20°C) as they would have lost some of their activity

Address for reprints: I. A. Mackie, Moorfields Eye Hospital, City Road, London EC1V 2PD

at temperatures above 4°C. The standards used for the plate assay were checked monthly on the spectrophotometer, against the calibration curve, to assess whether they had lost any activity.

Results

A straight line graph was obtained between the logarithms of the total quantities of the HEL in µg on the discs and the squares of the diameters of the zones of lysis of *M. lysodeikticus* on the plate, in the range equivalent to that in human tears (Fig. 1); a non-lysozyme antibacterial factor has been described in human tears (Friedland and others, 1972). It has been neither identified nor assayed, and it has not been taken into account in this method.

A straight line graph was obtained with the HEL calibration on the spectrophotometer (Fig. 2) (Parry and others, 1965). A decrease in absorption during the first minute of 0·030 was obtained by 1 µg HEL/ml buffer-substrate, under stated conditions. This represented, by our definition, 30 'units of activity'/µg HEL (30 000 units/mg).

It was necessary for the standard HEL, which was used in the test, to be calibrated in the laboratory. Lysozyme chloride ex egg white* was stated to have an activity of approximately 15 000 units/mg. On repeated testing of freshly prepared solutions, however, an activity of 30 000 units/mg was recorded.

The lysozyme concentration in units of activity/µl tear fluid, of the normal eyes of 54 volunteers (aged 18 to 86 years) was assayed (Fig. 3). The mean level of this distribution decreased by one unit of activity/µl tear fluid for each year. A limit of 70 units of activity/µl tear fluid at 20 years of age had decreased to 40 units/µl tear fluid by 85 years, and this was considered to represent the lowest normal concentration, although one in 108 eyes lay below it; it is called the critical limit.

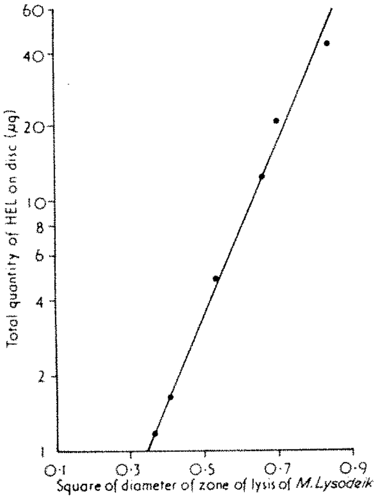

FIG. 1 *Calibration graph of HEL on plate of* M. lysodeikticus

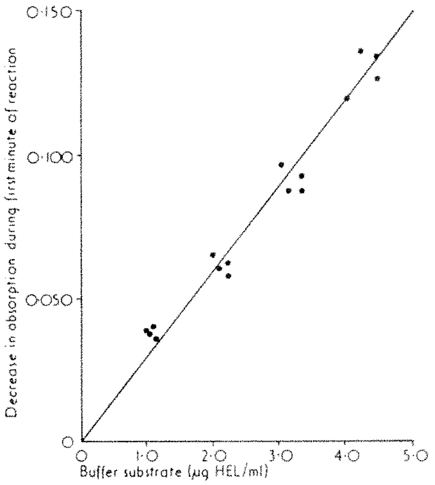

FIG. 2 *Calibration graph of HEL on spectrophotometer*

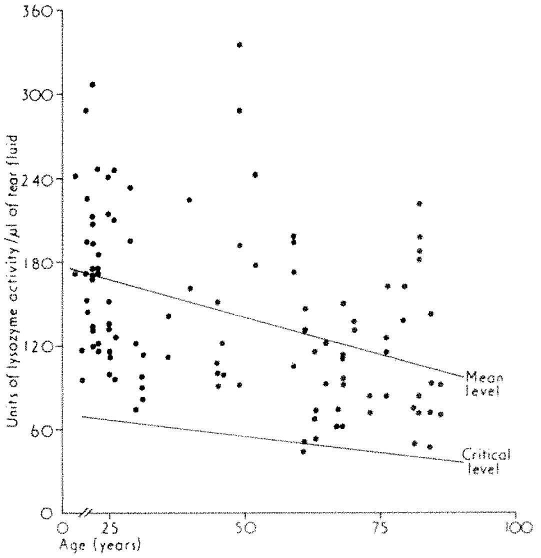

FIG. 3 *Lysozyme concentration by age in 54 normal subjects*

The variability of the volume of tear fluid absorbed by the Whatman filter paper discs, which were considered 'wet' on inspection, is shown in Table 1. In all age groups, the volume collected on a 'wet' disc could vary by threefold, and between

*Supplied by Koch-Light Laboratories

Table I *Volume of tear fluid absorbed on to filter-paper discs from 54 normal volunteers*

Age-group (years)	*No. per group*	*Range of volume (µl)*	*Mean (µl)*	*Standard deviation*
20–39	24	2·0 to 8·5	5·1	1·5
40–59	9	2·3 to 6·5	4·5	1·2
60–89	21	2·2 to 6·5	4·3	1·2

the ages of 20 and 40 years, by fourfold. The mean volume collected varied from 5·1 µl for 20 to 39 years of age to 4·3 µl for 60 to 89 years.

Out of 54 normal volunteers, four were slow in their response to produce enough tear fluid to wet the disc, and 11 were quick, producing copious quantities of tears, see Fig. 4. The other volunteers were classified as 'medium tear producers'. It was demonstrated that tear fluid produced slowly could have a high or low normal lysozyme concentration, as was also the case for tear fluid produced quickly and copiously.

There was no relationship between the lysozyme concentration, measured in units of activity/µl tear fluid, and the total quantity of tear fluid absorbed by the disc (correlation coefficients: –0·1 for left eye, –0·1 for right eye) (Fig. 5). This meant that volunteers producing smaller quantities of tear fluid (2 to 3 µl absorbed by the disc) might have a high or low normal lysozyme concentration. This was also the case for volunteers producing larger quantities of tear fluid (6 to 7 µl absorbed by the disc).

A significant association between the lysozyme concentration in the left and right eyes of the volunteers was calculated (correlation coefficient: 0·7).

The details of six patients with a clinical diagnosis of keratoconjunctivitis sicca, and three control patients with severe autoimmune disease, but with normal eyes, are summarized in Table II. Five out of the six patients with keratoconjunctivitis sicca had tear lysozyme concentrations well below the critical limit for the lowest normal concentration for their age; one, with quiescent systemic lupus erythematosus and keratoconjunctivitis sicca, had a lysozyme concentration around the limit. The three control patients had lysozyme concentrations well above the critical limit.

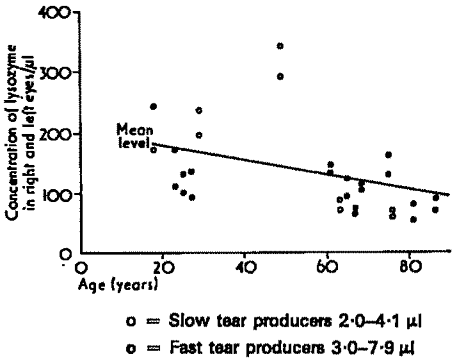

FIG. 4 *Comparison of lysozyme concentrations in slow and fast tear producers*

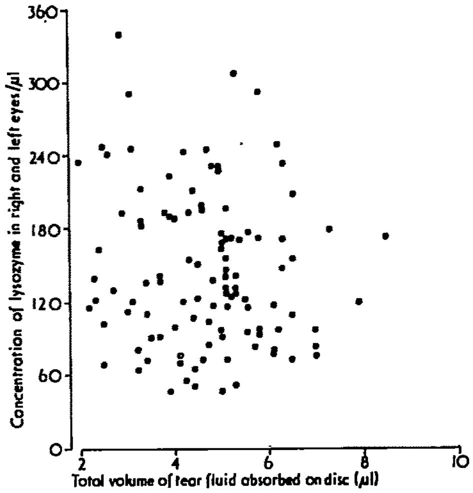

FIG. 5 *Total volume of tear fluid absorbed by disc compared with lysozyme concentration*

Discussion

Bonavida and Sapse (1968) stated that the variables affecting the diameter of the zone of lysis of the *M. lysodeikticus* include incubation time, temperature, concentration of micrococcus, and thickness of agar. Bijsterveld (1974) investigated different media for growing the *M. lysodeikticus* in order to find a medium on which to standardize the test. Pietsch and others (1973) stated that the reporting of results, compared with a lysozyme standard, was not necessary because the zone of lysis obtained with a standard might be erroneous because of impurities.

In our experience the growth of the *M. lysodeikticus* on DST agar (1·2 per cent Oxoid) is never exactly the same, and direct comparison between zones of lysis is unreliable. It is only by direct comparison with a reliable standard on each plate that the biological variable (that is the growth of the *M. lysodeikticus*) can be compensated. If the lysozyme standard is calibrated on the spectrophotometer into units of activity, compensation can be made for impurities and different strengths.

Table II *Clinical details of six patients and three controls*

	Age of patient (years)	*Diagnosis*	*Volume of tear fluid*		*Lysozyme concentration (units/µl)*	*Critical limit* (units/µl)*
			Eye	*(µl)*		
Sicca syndrome	23	Hypergammaglobulinaemia with sicca	Right	2·5	39	69
			Left	2·4	39	
	33	Quiescent systemic lupus erythematosus and sicca	Right	4·0	60	65
			Left	2·5	71	
	52	Sicca	Right	6·2	15	56
			Left	4·8	15	
	60	Sicca	Right	5·6	24	52
			Left	4·2	30	
	66	Sicca	Right	2·9	<9	49
			Left	2·4	<9	
	82	Sicca	Right	3·6	19	41
			Left	1·8	44	
Controls with other autoimmune diseases	54	Severe rheumatoid arthritis Normal tear film and eyes	Right	2·9	87	55
			Left	2·4	72	
	55	Raynaud's disease Scleroderma Skin biopsy positive for systemic lupus erythematosus Normal tear film and eyes	Right	2·8	84	54
			Left	4·0	120	
	67	Sjögren's syndrome (dry mouth and rheumatoid arthritis) Normal tear film and eyes	Right	2·7	64	48
			Left	2·2	78	

*Lowest normal level for age

It is essential to weigh the filter paper discs to estimate the quantity of tear fluid absorbed. Otherwise, the diameter of the zone of lysis of the *M. lysodeikticus* will be increased by 40 per cent for each doubling of the quantity of tear fluid on the disc.

Erickson (1955) and McEwen and Kimura (1955) reported the absence of lysozyme in the sicca syndrome, and Minton (1965) reported its absence in one case of systemic lupus erythematosus, with some reduction in other cases.

We have shown in this study that the tear lysozyme concentration is likely to be abnormal, if it lies below a critical limit, which varies with age.

Bijsterveld (1973) found that the probability of misclassification of a patient with keratoconjunctivitis sicca by Schirmer's test was 15 per cent, by rose bengal test 5 per cent, and by his lysozyme method 1 per cent. Pinschmidt (1970) showed that Schirmer's test was inconsistent. We suggest that the tear lysozyme concentration, in units of activity/µl tear fluid, provides the ophthalmologist with a good guide to lacrimal gland function.

Summary

An accurate method of assaying the tear lysozyme concentration in units of activity/µl has been developed. Normal physiological levels which vary with age have been determined.

It has been demonstrated that measurement of the volume of tear fluid collected and assay with a calibrated standard are essential for the accurate determination of the precise concentration of lysozyme in the tear fluid.

Tear lysozyme concentration can be used as an index of lacrimal gland function, and in the diagnosis of the sicca syndrome and associated conditions.

We believe that this method of tear lysozyme assay has important applications in drug toxicity states in humans (for example, practolol toxicity) and also in animal drug toxicity studies.

We wish to thank Dr H. Cleeve for advice on chemistry, Mrs A. Clewer for advice on statistics, and Dr D. Fleck, Dr H. Ross, and Mr B. Chessum for advice on bacteriology.

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Correspondence

Fluorinated steroids

TO THE EDITOR *British Journal of Ophthalmology*

SIR, Many ophthalmologists must have heard or read by now of the adverse effect on the skin of the prolonged use of fluorinated steroids, such as betamethasone, fluocinolone, and fluocortolone 21-hexanoate. It has been said that the fluorine present induces neovascularization and dilatation (telangiectasia) and ruptures the dermal collagen and follicular epithelium. These adverse changes are reversed by using hydrocortisone. Despite this finding which originated in 1969 I do not know of any statistically significant account of a similar effect on the eye. In two cases of postherpetic disciform keratitis in which drops of betamethasone were prescribed for a year, and in one case where the same drops had been prescribed daily for two years by a general practitioner for conjunctivitis sicca, I found many substantial dilated vessels in the corneal stroma associated with a highly irritable eye. There was no other pathological feature. On changing to drops of hydrocortisone 1 per cent, the symptoms were relieved and after one week most of the corneal blood vessels had become emptied.

Yours faithfully,

F. C. RODGER

Princess Margaret Hospital,
Swindon,
Wiltshire

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Aqueous humour lactic dehydrogenase isoenzymes in retinoblastoma

(*Brit. J. Ophthal.* (1975), 59, 268)

TO THE EDITOR *British Journal of Ophthalmology*

SIR, Since our paper was published last May we have become aware of additional relevant information we wish to bring to your attention.

We have had the opportunity to study two patients in whom aqueous humour assays were at variance with our previously-reported findings. One patient, with histologically proven retinoblastoma, had a total aqueous humour lactic dehydrogenase (LDH) of 2303 iu/l and a ratio LDH$_5$:LDH$_1$ of only 1·9. The other patient, with bilateral, congenital non-rhegmatogenous retinal detachment and no retinoblastoma, had total aqueous humour LDH levels of 194 and 19, and ratios LDH$_5$: LDH$_1$ of 24 and 30!

A recent paper by Swartz, Herbst, and Goldberg (1974) supported the original hypothesis of Dias, Senthe Shanmuganathan, and Rajaratnam (1971) that retinoblastoma was associated with a raised total aqueous humour LDH, and they referred to a paper (Kaneko and Suzuki, 1972) in which the authors found (as we did) that, although the total aqueous humour LDH was inconsistently raised in retinoblastoma, in seven cases it was associated with an elevated LDH$_3$ isoenzyme (and to a lesser extent LDH$_2$ and LDH$_4$ fractions).

We believe that the aqueous humour LDH assay is currently a valuable diagnostic adjunct in the diagnosis of retinoblastoma, in that both an absolute elevation of the total aqueous humour LDH and a relative elevation of the slow isoenzyme fractions (that is, a 'shift to the right') appear to be suggestive but not diagnostic of retinoblastoma. We wish to encourage further experience with this test to resolve the inconsistencies in the literature, and to define the limits of reliability and the scope of application of this biochemical assay.

Yours faithfully,

PAUL E. ROMANO and JACK KABAK

Department of Ophthalmology,
Northwestern University Medical School,
Chicago, Illinois

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Corneal epithelial oedema

TO THE EDITOR *British Journal of Ophthalmology*

SIR, Over many years some difficulty has been experienced during prolonged three-mirror examinations because corneal epithelial oedema tended to supervene after a few minutes. The solutions being used at this hospital were 1, 2, or 3 per cent hydroxypropyl methyl cellulose (HPMC) in water with phenyl mercuric nitrate 0·002 per cent.

It occurred to us that due to the large size of the HPMC molecule, the osmotic effect of such a solution was almost identical to that of water, hence it was a likely cause of the epithelial oedema.

Accordingly, HPMC was made up in 0·8 per cent sodium chloride instead of pure water.

This solution appears completely to have resolved the problem. The cornea remains crystal clear throughout the most prolonged examination. We thought this information would be of interest and value to readers.

Yours faithfully,

J. H. REDMOND SMITH and R. WATKINS

Moorfields Eye Hospital,
City Road,
London EC1V 2PD

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Book reviews

Contact Lens Practice: Hard and Flexible Lenses. By R. B. MANDELL, 2nd ed. 1974. Pp. 819, figs, tables, refs. Thomas, Springfield, Illinois ($32·50)

A book that has been reprinted five times in its first edition has obviously filled a need.

The 2nd edition of Professor Mandell's book has increased in size, but most of this increase is taken by new chapters on flexible lenses. Contributors include seven American optometrists, an American ophthalmologist Dr Antonio Gusset who describes the therapeutic use of soft lenses, and gratifyingly Professor Robert Fletcher of the City University London who gives an account of scleral hard lenses.

The book is described as a contact lens fitting guide for practising ophthalmologists and optometrists and a comprehensive guide for students. It achieves this aim, is well written and easily readable. More information about the vitally important water content of continuously worn soft lenses is needed.

Excellently printed, bound and illustrated, this book represents good value in dollars although the sinking pound makes it more expensive for UK purchasers.

M. O'RIORDAN

Contact Lens Practice: Visual, Therapeutic and Prosthetic. Pp. 368, 382 figs (18 colour plates), tables, refs. 1975. Baillière Tindall, London (£19·50)

The arrival of the first edition of *Contact Lens Practice* is an event keenly awaited by all those with an interest in this field. There can be no disappointments since this book is a masterly production and Montague Ruben and his contributors have written a balanced comprehensive text covering all aspects of contact lens practice. It contains a wealth of information and the up-to-date knowledge will prove useful to the established contact lens practitioner and the novice alike.

The book consists of 15 clearly written chapters, each with an extensive bibliography. In addition a useful appendix and a comprehensive index have been included.

The author begins with an interesting summary of the history and evolution of contact lenses. This chapter is followed by one dealing with indications for contact lens wear. All the principles appertaining to the management of therapeutic cases with contact lenses are discussed. An exhaustive list of specific diseases, treatable with contact lenses could have been included with benefit, even though they are discussed in a later chapter.

The next chapter deals with tears, and with certain aspects of the physiology, anatomy, and pathology of the cornea, conjunctiva, and ocular adnexa, of immediate concern to contact lens practitioners. This discussion, with many photomicrographs, allows an easy understanding of these relevant topics. The following chapter provides concise basic information on optics in relation to contact lenses. Useful nomograms have been included, and formulae relevant to contact lens work explained. The succeeding chapter deals both with physical chemistry pertinent to contact lenses and all materials encountered in contact lens practice.

Accurate measurement of the corneal curvature is essential for correct lens fitting and the next two chapters cover this topic thoroughly. The following few chapters deal extensively with the fitting of corneal, scleral, and soft lenses; patient management; intolerance and eye disease resulting from contact lens wear.

Special diseases for which contact lenses are indicated are discussed in detail; these diseases which require special consideration when fitting lenses, include keratoconus, aphakia, bullous keratopathy, postkeratoplasty, dry eyes and tear anomalies. The chapter on manufacturing techniques is useful for the contact lens practitioner since he should be aware of the limitations imposed by manufacturing techniques. The final chapter deals fully with ocular cosmetic and prosthetic appliances.

It is a difficult task to produce a work of this quality, when the field is advancing rapidly and when there exists a wide range of techniques and opinions. However, the author has succeeded admirably and it is difficult to find fault with this book. I would have preferred a chapter to deal specifically with soft contact lenses, although all the relevant and current information in this important development is covered, albeit, distributed in various chapters. Some illustrations and plates are without reference in the text but they are all relevant and self-explanatory.

This textbook is essential reading for all those who work with hard or soft contact lenses. It is likely to become the standard text for reference and study in this field.

R. DANIEL

The Diagnosis and Treatment of Cerebral Arterial Disease of Extracranial Origin. Edited by R. D. FINE. 1974. Pp. 203, figs, tables, refs. Australasia Medical Publishing, Glebe, NSW ($A15·00)

This book is concerned with embolism and carotid and vertebrobasilar disease in relation to their effects upon the cerebral circulation. It opens with concise accounts of cerebral vascular anatomy and physiology, and describes how the latter may be disturbed by disease. The mechanisms of ischaemic episodes are thoroughly discussed together with their clinical manifestations and how to investigate them.

The chapter on ophthalmic aspects of carotid and vertebrobasilar disease will be of particular interest.

The illustrations are unusually good and the references selective and well chosen. The typography is, however, somewhat faint and as some sections are in very small type it is not easy to read. JOHN MARSHALL

Differential Diagnosis of Intraocular Tumors: A Stereoscopic Presentation. By J. D. M. GASS. 1974. Pp. 371, figs. Mosby, St Louis; Kimpton, London (£34·45)

The series of American ophthalmological textbooks, which is being produced to provide a stereoscopic presentation of different aspects of the subject, has been greatly enhanced by the volume on the differential diagnosis of intraocular tumours under the authorship of Dr Donald Gass. As one of the pioneers of fluorescein angiography he has been able to associate clinical appearances, fluorescein studies, and the pathological findings in such a way that the reader cannot but achieve an excellent working knowledge of the problem.

The author's comment in the preface upon the indication of statistics at the Armed Forces Institute of Pathology that, of every five eyes with clear media enucleated for malignant melanoma, one proved to have an alternative pathological diagnosis, is a timely reminder of the importance of studying intraocular swellings in all their aspects. JAMES R. HUDSON

Diplopia. By ROBERT A. CRONE. 1973. Pp. 488, figs, bibl. Excerpta Medica, Amsterdam (approx. $60)

This excellent book deals in considerable depth not only with anomalies of binocular vision and disturbances of ocular motility but also with the physiology and anatomy of the development of binocular vision based on evolution and including the kinematics and control of eye movements.

The clinical problems are extensively illustrated by well-documented details relating to a large number of patients personally examined and for the most part treated by the author himself all of which will be of considerable interest to the practising ophthalmologist.

The division of each page into two parallel sets of print is attractive and makes for easy reading. The case photographs are clear and so are the fields of binocular fixation. The simplified Hess charts are for the most part adequate except where they are only reproduced in a cruciform manner as in Case 12.33 page 267 which does not sufficiently illustrate the deviation.

The book covers most aspects of binocular anomalies of all types with special reference to ocular palsies. There is an excellent chapter on orbital lesions causing diplopia in which is included diplopia after operations for retinal separation.

The retraction syndrome is well described and it is interesting to read that the author considers that 'anatomical abnormalities predominate in some cases and paradoxical innervations in others', in connexion with which he cites a case in which the abducent nerve was missing and the external rectus was supplied by a branch of the third cranial nerve.

The chapter on diseases of the ocular muscles including dysthyroid ophthalmopathy is excellent.

Dr Crone has included a most useful bibliography with some 1580 references but the subject index is short and not really adequate if the reader wishes to refer quickly to a particular topic.

The emphasis throughout the book is on clinical examination and diagnosis rather than on detailed methods of treatment, although the general principles of therapy are clearly stated.

There is very little reference to the problems relating to young infants suffering from squint nor of the special methods of assessment of their visual function.

Some of the most interesting material is to be found in the last three chapters which deal with convergence disturbances and diplopia of supranuclear origin, diplopia resulting from acquired disturbances of fusion, and uniocular diplopia.

This is certainly a book which should be read by all ophthalmologists interested in neuro-ophthalmology as well as those who are primarily concerned with the problems of strabismus. T. KEITH LYLE

The Eye (Comparative Physiology) Vol. 5. Edited by H. DAVSON and L. T. GRAHAM. 1974. Pp. 528, figs, tables, refs. Academic Press, New York (£21·60)

This is the first of two volumes on this subject. The book is planned to allow the authors to discuss specific types and is, therefore, not a generalized account. Such an approach has the advantage of making the book interesting and readable although the relationships of some of the topics to human physiology are necessarily obscure on occasion.

The first chapter deals with the vascular supply of the eye. The wide variety of vascular arrangements to ensure that the optic nerve and retina receive adequate blood supply are discussed, including the blood supply of the optic nerve in man. The comparative aspects of the intraocular fluids are discussed in the second chapter, and the extensive tables will be of value to workers in this field.

The third chapter deals with the authors' views concerning the mechanism of aqueous outflow based on electron-microscopic appearances. Intermittent vacuolar transcellular pores are considered to be the fundamental mechanism of aqueous transport through the trabecular mesh work and many excellent photographs are used to support this view. Chapter four deals extensively with the physiology of lens membranes, and a useful account is given of our present knowledge of the membrane structure of the lens. In chapter five the author discusses the methods whereby lens protein is examined and compared in different species. A valuable assessment of the method is given and the need for the consideration of other features, such as accommodation, which modify the properties of lens proteins is stressed.

This book is of particular value to research workers who wish to have an easily readable account of the particular topics discussed. An extensive bibliography after each chapter also contributes to the ease of reference for further reading. R. FISHER

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Notes

Symposium on Retinal Diseases

New Orleans, 6 *to* 10 *March* 1976

The New Orleans Academy of Ophthalmology 25th Anniversary Symposium on Retinal Diseases, presenting recent advances in diagnosis and management of vitreous surgery, diabetic retinopathy, and macular diseases, will be held in the Marriott Hotel, New Orleans. For further information write to Bonnie Cronè, Executive Secretary, New Orleans Academy of Ophthalmology, 515, Audubon Building, 931, Canal Street, New Orleans, LA 70112, USA.

Irish Ophthalmological Society

Dublin, 29 *to* 30 *April* 1976

The Irish Ophthalmological Society will hold its annual meeting in Dublin. The Montgomery Lecture will be delivered in Trinity College on the afternoon of 29 April by Professor H. Harms of Tübingen.

3rd Congress of the European Association for Maxillo-Facial Surgery

London, 6 *to* 11 *September* 1976

The 3rd Congress of the European Association for Maxillo-Facial Surgery will be held at the Royal College of Surgeons of England, London. All topics relating to the field of Maxillo-Facial surgery will be covered. Application forms are obtainable from: Congress Secretariat, 3rd Congress EAMFS, 100 Park Road, London NW1 4RN.

International Symposium on Computer Assisted Tomography

Bethesda, 12 *to* 15 *October* 1976

An international symposium on computer assisted tomography in non-tumoural diseases of the brain, spinal cord and eye, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke, will be held at the Clinical Center on the campus of the National Institutes of Health, Bethesda, Maryland, under the chairmanship of Giovanni Di Chiro, MD.

Those interested are invited to submit detailed and documented abstracts (data, illustrations) by 1 August 1976, to Giovanni Di Chiro, MD, National Institutes of Health, Section on Neuroradiology, Clinical Center, Room 2D13, Bethesda, Maryland 20014, USA.

XXIII International Council of Ophthalmology

Tokyo, 14 *to* 21 *May* 1978

The main themes will be the pigmentary epithelium (including clinical and biochemical aspects and electron microscopy), and ocular immunology.

Obituary

B. M. Chatterjee

Professor B. M. Chatterjee died on 8 June 1975. A graduate from Calcutta Medical College in 1938 he became a Fellow of the Royal College of Surgeons of Edinburgh and England in 1953. He retired from the West Bengal Government Health Service as Professor of Ophthalmology in 1971 and became an Emeritus Professor at the NRS Medical College, Calcutta. In 1972 he was made a Fellow of the American College of Surgeons.

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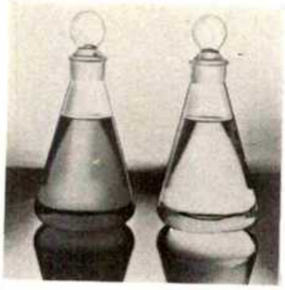

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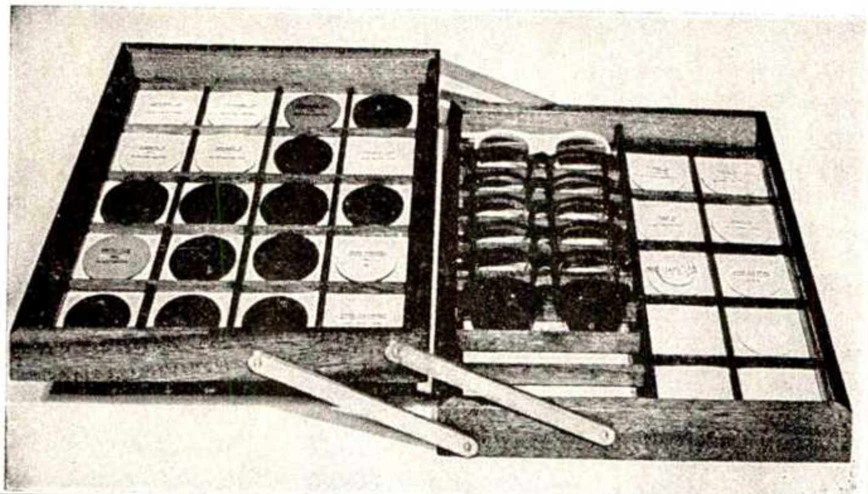

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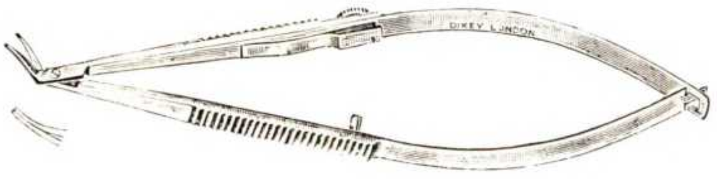

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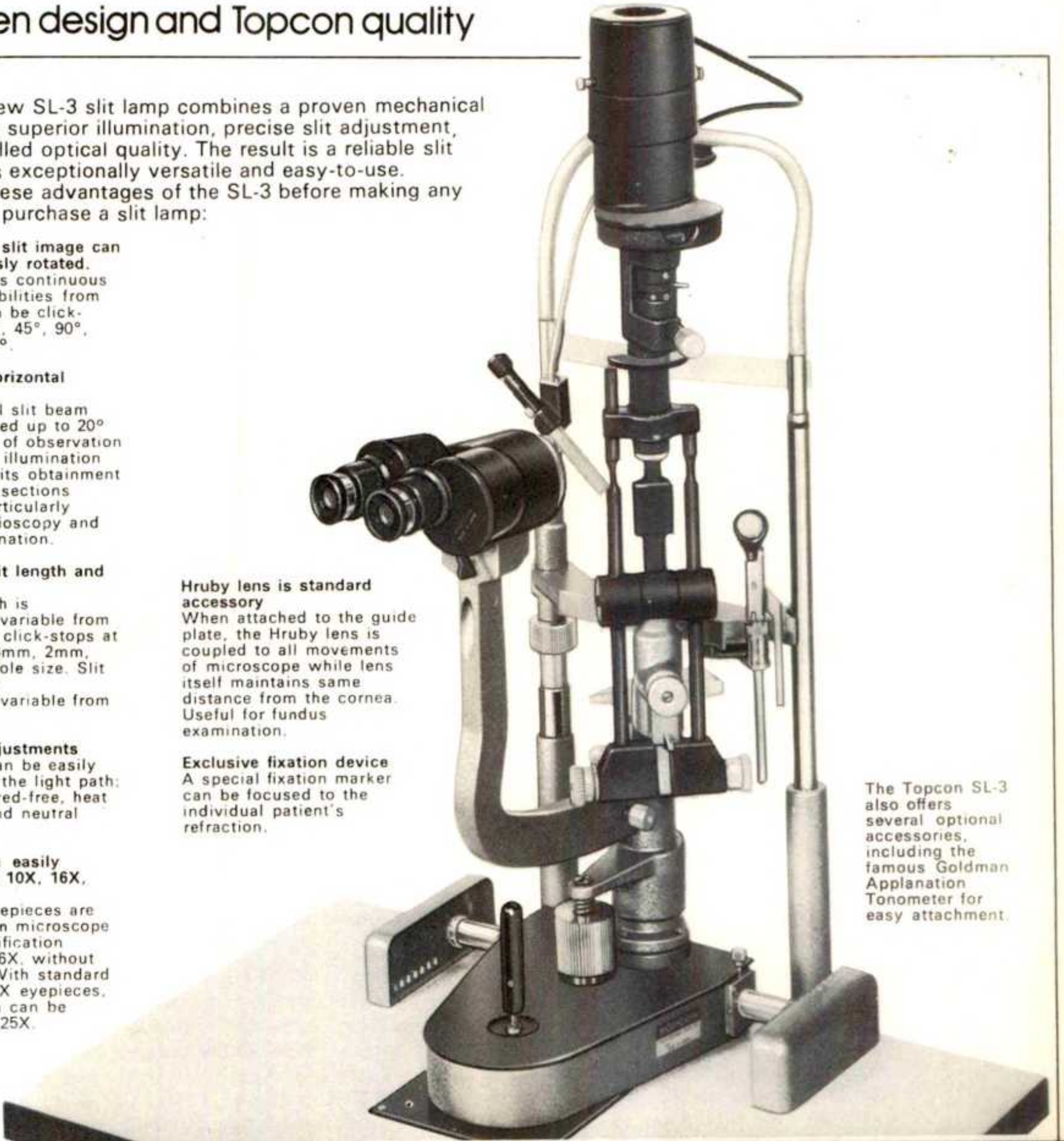

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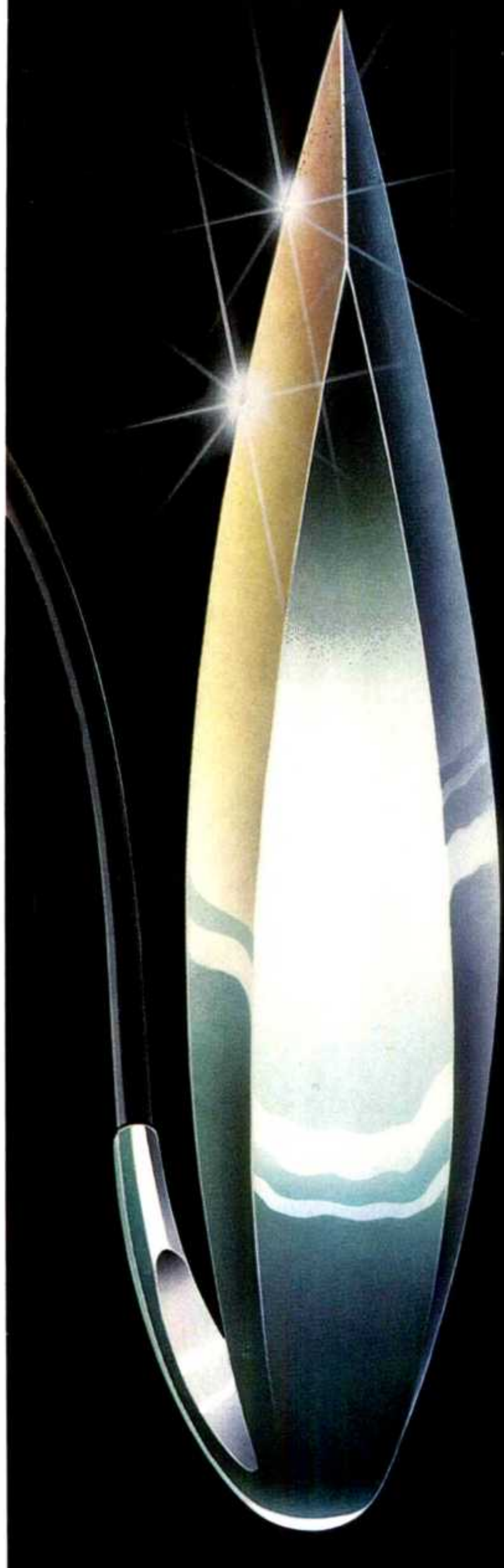

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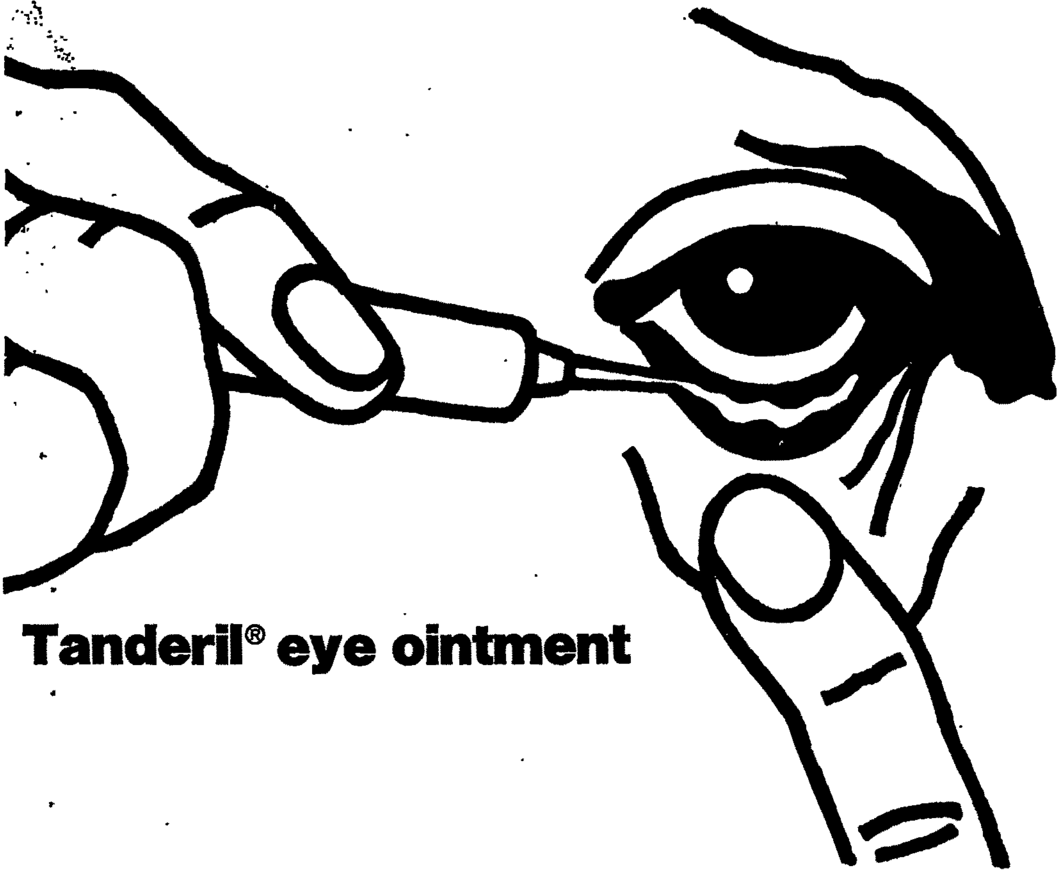

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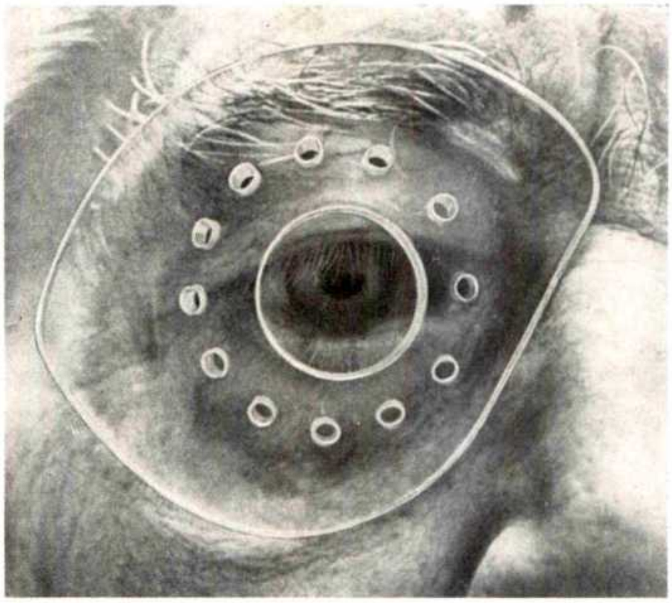

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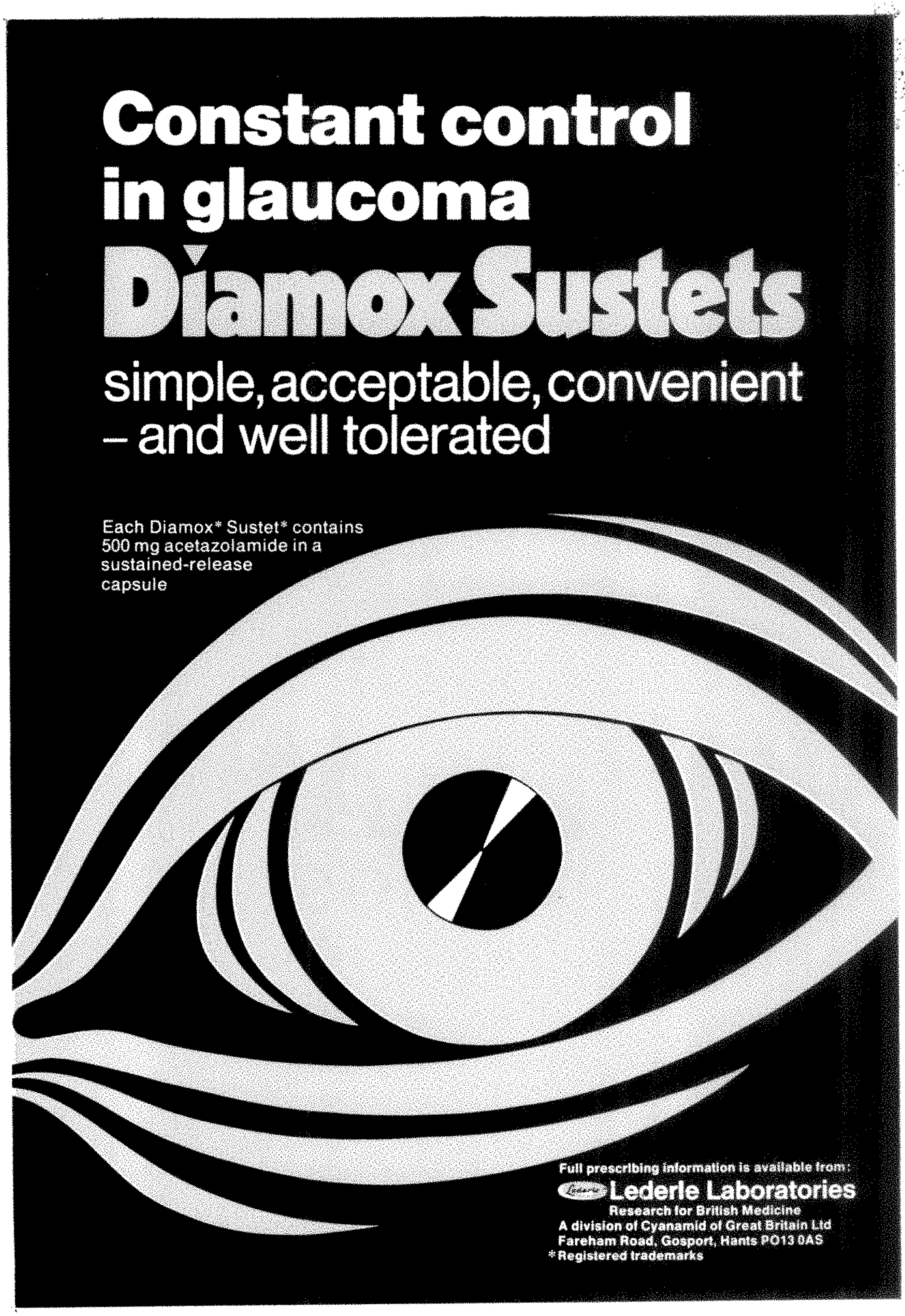

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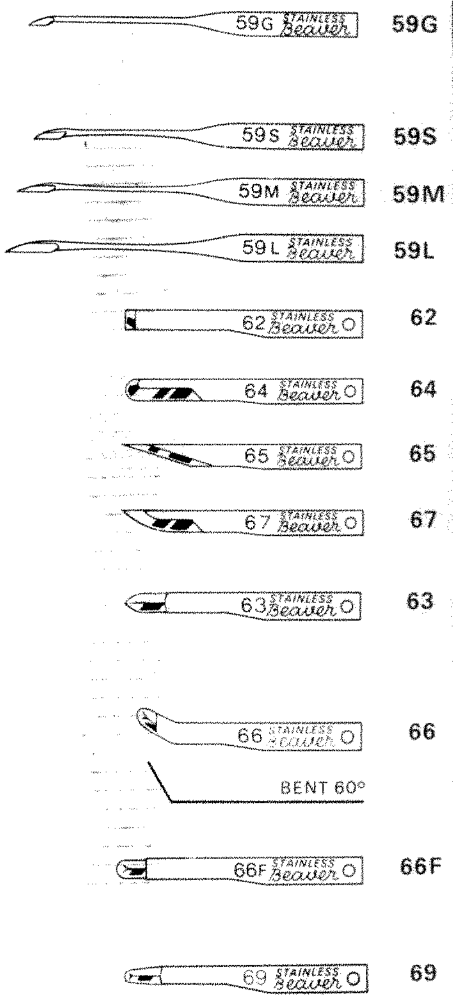

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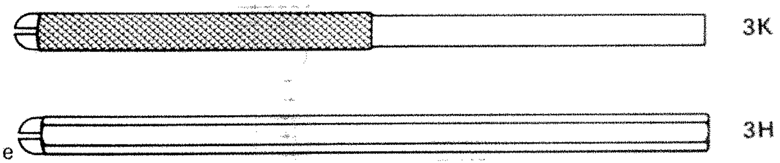

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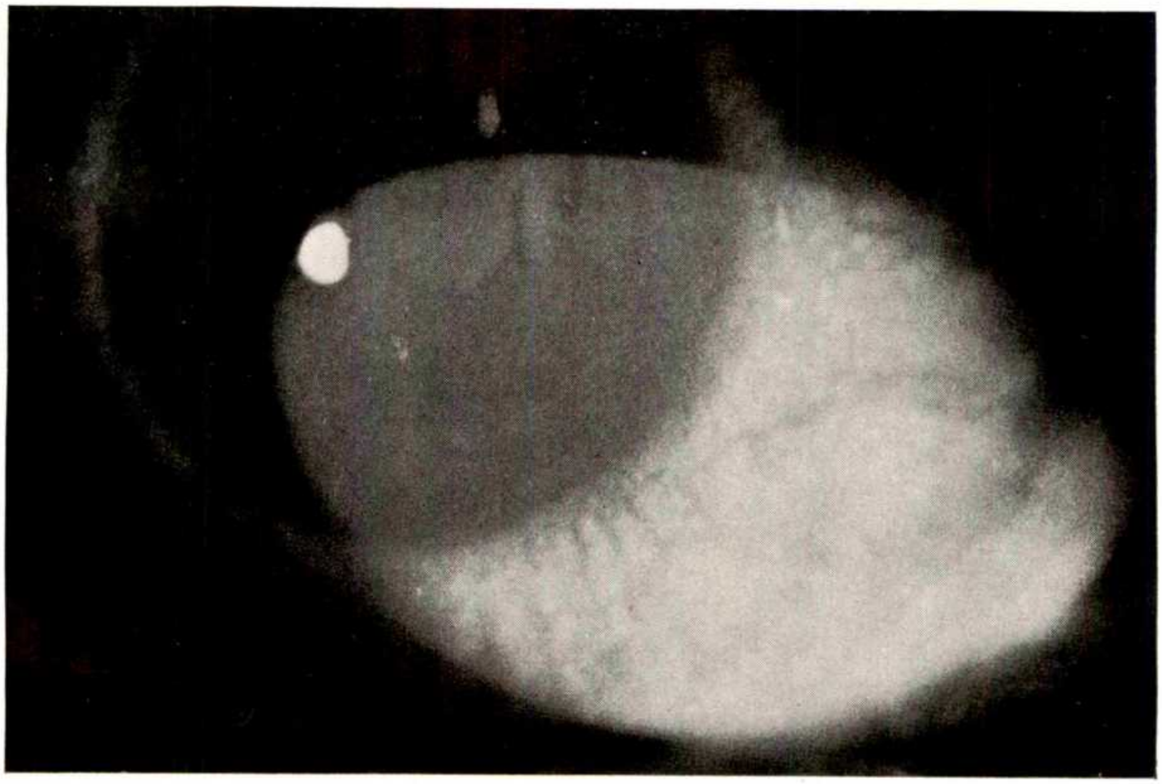

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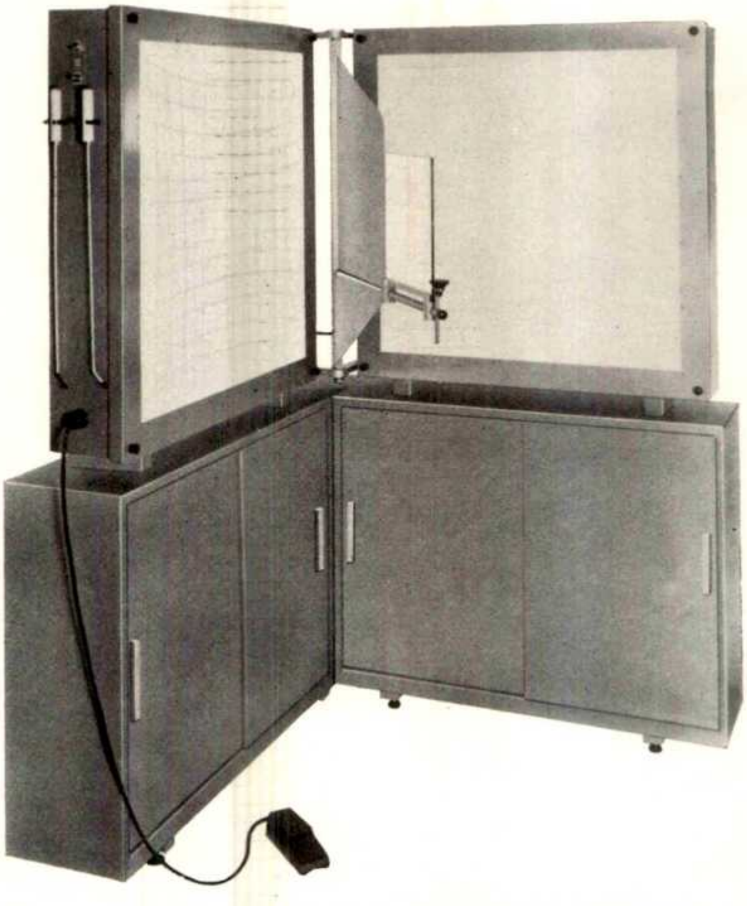

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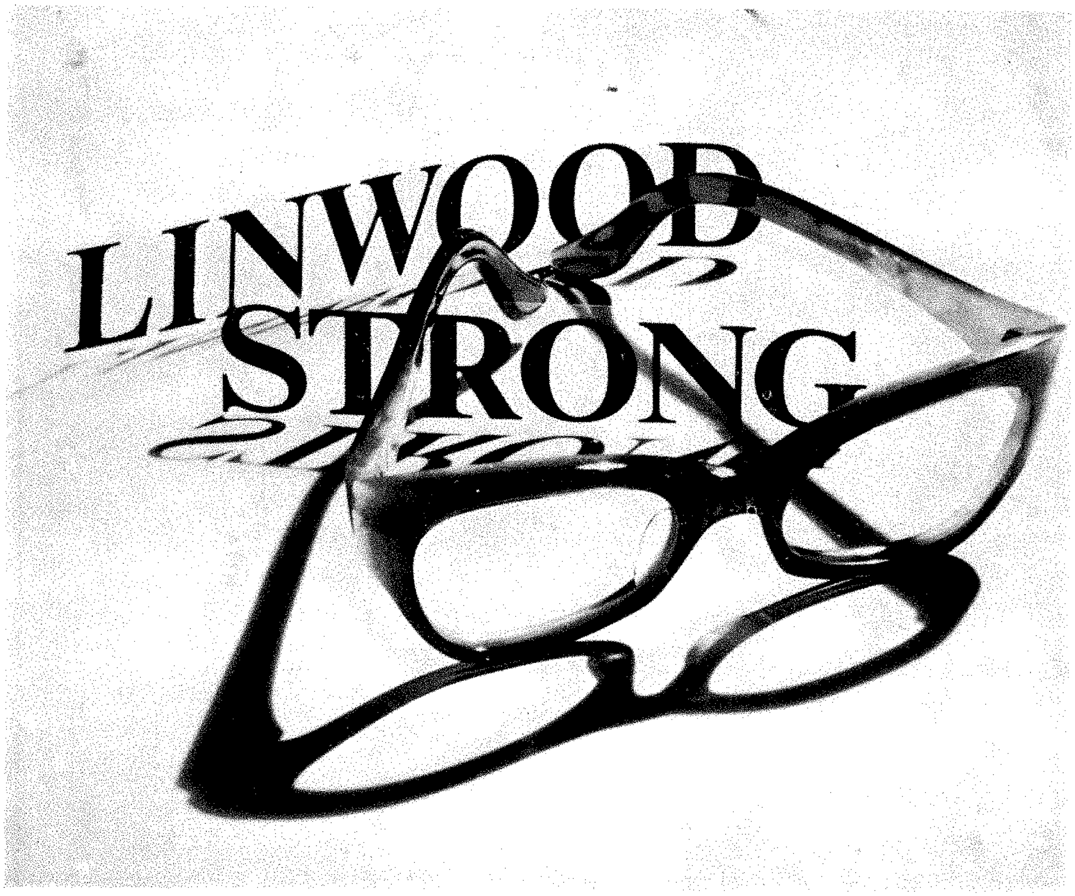

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William Charles Wells, 1757–1817

Eye physician

SIMON BEHRMAN
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Two hundred years ago—in the autumn of 1775—William Charles Wells sailed from Carolina to England. Wells explained his departure from America as follows:

> A paper, called 'An Association' had been offered for signature to all the male inhabitants of Charlestown above sixteen years of age. The subscribers to this bound themselves to obey implicitly certain authorities unconnected with the government of the country. I was one of the very few who refused to put their names to it. I was determined that my entrance into manhood should not be marred by what appeared to me an act of treason and rebellion. I was consequently obliged to leave Carolina.

Wells was met by his father

> whose conduct as a printer of a newspaper in Charlestown had become extremely offensive to the people of Carolina from his constantly maintaining the cause of royalty, and who found it prudent (a few years earlier) to leave that country and to return to Great Britain.

Shortly after arriving in England young Wells went to Edinburgh to begin his medical education.

The memoir, which Wells wrote at the end of his life, and his other writings are a rich source of biographical material (Wells, 1818).

The memoir begins with the following bare statement:

> I was born in Charlestown, South Carolina, in May 1757, being the second son of Robert and Mary Wells, both natives of Scotland.

He tells us that at the age of 14 years he was placed as an apprentice with Dr Alexander Garden,

> the chief practitioner of physic in Charlestown,

who was also a well-known naturalist. Among the many plants indigenous to America which Garden had sent to Europe was a species of magnolia he wished to have named after himself–Gardenia. As this name had already been applied to a Cape Jasmine, Garden had to make do with Gordonia. In the War of Independence Garden had supported the views of Great Britain and because of his loyalty he too had had to leave New England. In 1783 he settled in London in Cecil Street, Strand.

After passing the 'preparatory trials' for the degree of doctor in medicine in 1778, there followed in Wells's life years packed with adventure which only abated in 1785 when he returned to London and 'had the name of Dr Wells affixed upon the door of the lodging which I had hired'.

In 1779 he was offered and accepted a surgeoncy in a Scottish regiment in the service of Holland.

> For some time I felt myself pleasantly situated in the regiment, but the colonel who had been promoted to his command, merely from being an officer in the Dutch guards and bearing a Scotch name, Hamilton, but scarcely able to speak English, soon began to find fault with my conduct and in consequence confined me several times in a military prison. This behaviour, it may well be supposed, could not be borne by a high-spirited Englishman. I therefore resigned my commission and upon the very day of receiving my dismissal from the service, I attacked him openly in the street, and dared him to fight me; he became furious and ordered a file of musqueteers to seize me and carry me to prison.

When a few days later it was established that

> surgeon Wells was no longer an officer in the service

he was released.

> There is no doubt that the natural warmth of my temper urged me to do what might have appeared to another person rash . . . Charlestown was now in the possession of His Majesty's forces, and I returned to it for the purpose of collecting the scattered remains of my father's fortune. While there, though exempt by my profession from military calls, I made an offer of my personal services to the commandant of the town and was appointed an officer in a body of volunteers who by performing a part of the duty of the garrison, enabled a greater number of the regular troops to take the field than could have done so, without such aid. When Charlestown was abandoned by the King's forces, I went to East Florida. Shortly after my arrival there, apprehension being entertained for the safety of the province, I requested permission from the governor to assist in its defence and I received from him the command of a Company

This paper is based on a communication made to the Eye Physic Club, London, in November 1975

Address for reprints: Simon Behrman, FRCP, MRCS, 33 Harley Street, London W1N 1DA

> of volunteers. In 1783 I received a letter from my father in which he requested me, now that preliminaries of peace were signed, to go again to Carolina for the purpose of looking after his affairs. I accordingly went to Charlestown, furnished with a flag of truce which in previous intercourse between the two countries during the war, had always been regarded as a sufficient security against any attempt upon the liberty of the person who bore it. Immediately upon my arrival in Charlestown I was arrested. I refused to give bail on the ground that this would be deserting the security I had obtained by the flag of truce. My refusal proved most fortunate. For the night after my committal to prison a numerous mob assembled before the house in which I had been staying, demanding that I should be surrendered to them. I remained in prison upward of three months during which time I was robbed by another prisoner, and in consequence of my complaint of this, was most grossly abused by my jailor in a publication which began thus: 'William Charles Wells, a political sinner of the first magnitude in this land, and now suffering but a very small proportion of those pains and penalties which his high crimes and misdemenours have so justly deserved, in the common gaol of this metropolis' etc. Nature had not formed, nor education trained me to submit with silence to oppression. By means of money I got a letter inserted in one of Charlestown's newspapers.
>
> 'Charlestown
> in Gaol
> July 17 1783.
>
> For a freeman to be deprived of his liberty, and lodged in a common gaol; to be kept constantly locked up in a room whose ceiling is in that condition that the rain pervades it in every shower, sometimes in such quantity that it must be carried out in pails, and whose only window which is not being glazed, obliges him to exclude the cheerful light of day, at the same time that he shuts out the storm; lastly to be without friends whom the dread of popular resentment prevents from visiting him; if these sufferings are but a small portion of what he is to bear he can look forward to nothing but death. Grant him but the choice of the mode, and he will thank Heaven for the opportunity of demonstrating his attachment to his sovereign'.
>
> A government vessel then arrived at Charlestown bringing a commissioner to demand my release. As soon as this affair was terminated I embarked with the commissioner in the vessel which had brought him to Charlestown and proceeded to St Augustine. The master ran his vessel aground upon rocks which had previously occasioned the loss of many vessels. She immediately bulged, and lost her mast and it was expected that her deck would separate from her ribs and be carried out to sea. With some other of the passengers, I had stripped myself completely naked and lashed myself to the capstan in order not to be washed away by the waves. The wind, however, became moderate and the accident which was dreaded did not happen.

A few hours after he was taken off the rocks

> the vessel went entirely to pieces.
>
> I embarked at St Augustine for Great Britain in the month of May 1784.

In the following year Wells established himself in Serjeants' Inn, Fleet Street.

> I soon found that I was a good deal unfit for early success in my profession in London; for I entertained a very high notion of its dignity, and felt a great contempt for most of the apothecaries with whom I became accidentally acquainted; in consequence I passed several years almost without taking a single fee. In 1790 I was fortunately chosen as one of the physicians to the Finsbury Dispensary; for I was now furnished with the means of studying medicine practically and received from the institution a gratuity of £50 annually. In 1795 I was elected assistant physician to St Thomas's Hospital, and in 1800 I became one of the physicians of it.

The quotations presented from his writings reveal Wells as a high-minded person who was also impatient and impetuous. He himself admitted to having a temper which was 'passionate and violent'. Wells noted another feature of his character: 'a practice of swearing when my feelings have been agitated and even sometimes when no excuse of this kind has existed'. Wells attributed this practice to which he was given since childhood, to the fact that he had lived up to the age of 11 years 'close upon the harbour of a large sea-port in America and by this means associated much with blackguard sailor boys'. This life-long tendency to compulsive utterances, often unprovoked, has some affinity to Gilles de la Tourette's syndrome.

Wells was admitted into the Royal Society one year after the publication in 1792 of his Essay on Vision. Wells, as well as his medical contemporaries, regarded it as a major contribution to science. Even as recently as 1928 (James, 1928) the essay was published almost in its entirety. The only comment made at the time was: 'Wells is chiefly to be remembered for his essay on single vision with the two eyes'.

Wells began the second part of his essay by stating: 'accidents often lead to discoveries which reason alone might not easily have reached'. He stumbled upon the discovery while carrying out numerous experiments on himself involving the induction of binocular after images. This involved looking steadily for some time at a flame of a candle so that when the gaze was then directed upon a white object, a coloured spot appeared upon it.

> I shall now relate some observations respecting the apparent directions of the spot.
>
> 1. The spot is always seen single, whether the surface, upon which it is projected, be touching the face or at the greatest distance from us. The fact indeed is so open to observation that I should

> scarcely have thought of mentioning it had not Dr Darwin lately told us that the spot is seen double as often as the eyes are directed to an object more or less distant than the luminous body which gave rise to it. I shall only say, that I have made the experiment, I believe, upward of an hundred times, uniformly with same result.
>
> 2. The spot not only appears single in every ordinary position of the optic axes, but cannot even be made to appear double by any means whatsoever. If it be projected, for example, upon a piece of white paper on pressing one eye upward or downward or to either side, the spot will appear single and to possess its former place on the paper, as seen by the eye, which is not disturbed. Before I knew the result of this experiment, I had imagined, that, the position of one eye being forcibly altered, the external situation of the spot would likewise be altered and the spot by consequence be seen double.

The third part of his essay is devoted to the formulation of a theory to explain these observations

> which reason alone might not have reached.

The ingenious theory need not be subjected to further scrutiny since the clue to Wells's preposterous observations is to be found in his

> 'Experiments and observations on several subjects in optics'.
>
> The vision of my left eye becomes imperfect if the object be moved to a greater distance than that of nineteen inches. I have by my right eye imperfect vision of all objects unless their distance is so great that the rays proceeding from them may be regarded as parallel.

There is, therefore, evidence of anisometropia of the type favouring the development of alternating vision, so that his right eye would have been used for distant vision and the left for near work. This functional defect would, of course, explain the absence of diplopia in the experiments he described.

It must be emphasized that, utilizing the same technique of binocular after-images, Wells made some extremely important observations.

> During a slight fit of giddiness I was accidentally seized with, a coloured spot occasioned by looking steadily at a luminous body, and upon which I happened at that moment to be making an experiment, was moved in a manner altogether independent of the positions of my eyes. I again produced the spot by looking some time at the flame of a candle; then turning myself round till I became giddy, I suddenly discontinued this motion, and directed my eyes to the middle of a sheet of paper fixed upon the wall of my chamber. The spot now appeared upon the paper, but only for a moment; for it immediately after seemed to move to one side, and the paper to the other, notwithstanding I conceived the position of my eyes to be in the meanwhile unchanged. To go on with the experiment, when the paper and spot had proceeded to a certain distance from each other they suddenly came together again; and this separation and conjunction were alternately repeated a number of times; the limits of the separation gradually becoming less till at length the paper and spot both appeared to be at rest and the latter to be projected upon the middle of the former, I found also that when I had turned myself from left to right, the spot moved from left to right; but when I had turned from right to left the spot would move from right to left.

These are observations which represent accurately the oculogyric illusions upon deceleration after rotation.

> I observed these appearances while I stood erect. When, however, I inclined my head in such a manner as to bring the side of my face parallel to the horizon the spot and paper would then move from each other, one upward and the other downward. But all these phenomena demonstrated, that there was a real motion in my eyes at the time I imagined them to be at rest.

Among the problems of visual perception which engrossed Wells was Priestley's observation that 'common air brightens the colour of blood'. Wells questioned Priestley's opinion that blood was

> fitted both to imbibe and to part with phlogiston, becoming black when charged with this principle but highly florid when freed from it.

Wells conjectured that the change in colour must be due to some change in the state of the 'red globules' of the blood. Wells proposed that the colour of the blood 'brightened' as a result of a change analogous to that which occurred

> to cinnabar in making vermilion. This pigment, it is known, is formed from cinnabar merely by subjecting it to a minute mechanical division. But the effect of this division is, to interpose among its particles, an infinite number of molecules of air which now acting as opake matter, increase the reflection of light from the interior parts of the heap, and by this means occasion the whole difference of appearance which is observed between those two states of the same chemical body (Wells, 1797).

Wells communicated his most important discovery to the Royal Society on 4 July 1811 (Wells, 1811).

> I was consulted upon a disease of vision, which, as far as I know, has not hitherto been mentioned by any author. The subject of it was a gentleman about 35 years old. About a month before I saw him, he had been attacked with a catarrh, and as this was leaving him he was seized with a slight stupor, and a feeling of weight in his forehead. He began at the same time to see less distinctly than formerly with his right eye, and to lose the power of moving its upper lid. The pupil of the same eye was now also observed to be dilated. In a few days, the left eye became similarly affected with the right, but in a less

> degree. Previously to his present ailment his sight had always been so good, that he had never used glasses of any kind to improve it. On examining his eyes myself, I could not discover in them any other appearance of disease, than that their pupils, the right particularly, were much too large, and that their size was little affected by the quantity of light which passed through them. At first, I thought that their dilatation was occasioned by a defect of sensibility in the retinas; but I was quickly obliged to abandon this opinion, as the patient assured me, that his sensation of light was as strong as it had ever been during any former period of his life. I next inquired whether objects at different distances appeared to him equally distinct. He answered that he saw distant objects accurately, and in proof told me what the hour was by a remote public clock; but he added that the letters of a book seemed to him so confused that it was with difficulty he could make out the words which they composed. He was now desired to look at a page of a printed book through spectacles with convex glasses. He did so and found that he could read it with ease. From these circumstances it was very plain that this gentleman at the same time that his pupils had become dilated and his upper eye-lids paralytic, had acquired the sight of an old man, by losing suddenly the command of the muscles by which the eye is enabled to see near objects distinctly . . .
>
> After I had reflected upon this case it occurred to me that, as the juice of the herb Belladonna, when applied to the eye, occasions the pupil to dilate considerably, and so become unalterable by light, an effect might at the same time be produced by it upon vision, similar to that which I have just described. I had, indeed, in the course of a few years applied Belladonna several times to my own eyes, without observing any change in my sight, beyond what I referred to the increased size of the pupils; but as I had not looked for any other, I thought it possible that some additional one might have happened without my having perceived it.

Because of his presbyopia Wells regarded his own eyes unfit 'for the experiments which I wished to be made with Belladonna'. He therefore applied 'the juice of Belladonna' to Dr Cutting's* left eye.

> Half an hour after when his pupil was but little dilated perfect vision commenced at a distance of seven inches; in fifteen minutes more it began at the distance of three feet and a half. When his pupil had acquired its greatest enlargement the distance was eight feet. This state of vision continued in its greatest extent to the following day; and it was not till the ninth day that he completely recovered the power of adapting his eyes to near objects. Dr Cutting remarked that after his pupil had nearly returned to its former size, his capacity of adapting the eye to different distances was still very limited. A great degree of dilatation may take place in the pupil without total want of power to adapt the eye to different distances. Though I could not doubt the accuracy of Dr Cutting's observations, yet as he was the first person who ever applied Belladonna to his eyes for the purpose which has been mentioned, and as the results were remarkable, I requested him to repeat the experiment with the other eye. He complied with my desire and found that the appearances which followed were similar. As the action of the external muscles of the eye has been frequently resorted to for an explanation of its capacity to see objects perfectly at different distances, I requested Dr Cutting to attend to this matter. He accordingly ascertained while his eye was in a natural state, the distance from his face of the nearest point at which he could make the two axes meet, this being the greatest trial of strength to which those muscles can be exposed. While in consequence of the application of Belladonna he was without power of adapting his eyes to different distances, he found that the strength of these muscles was not diminished. It follows therefore that the external muscles have little or no concern in fitting the eye to see distinctly at different distances.
>
> The only other part of the eye or its appendages which remains for enabling us to see equally well at very different distances is the crystalline; and that it does produce this effect either wholly or very nearly so is manifest from the necessity even young persons are under who have lost it, of using glasses of very different convexities for near and remote objects. But in what way this important office is performed by it seems still unknown. The learned Dr Young† indeed has supposed that the crystalline has the power of altering its figure; but the proof hitherto given in favour of this opinion appears very defective.
>
> In 1794 I attempted to submit its justness to the test of direct experiments by applying to the crystalline of oxen which had been felled from thirty seconds to a minute before, chemical and mechanical stimuli, and those of Galvanism and electricity; but in no instance was any alteration of figure or other indication of muscular power observed.

The mydriatic property of belladonna was, of course, well recognized for centuries, but Wells must be credited with the important discovery of its cycloplegic action. He fully appreciated that these two effects of belladonna were distinct as they 'were not inseparably connected'.

Wells was also first to give a correct explanation for the deposition of dew. This was based on many observations and experiments which were described in his 'Essay on Dew', for which he was awarded the Rumford Medal by the Royal Society. His writings reveal him as an acute observer, always striving to submit his theories to critical tests.

Sir Benjamin Brodie, one of his ablest medical contemporaries (Brodie, 1865), paid the following generous tribute to Wells:

'Dr Wells was one of the most remarkable persons with whom it has been my lot to be personally acquainted'. Although he admired Wells's intellect, Brodie could not refrain from noting his

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*Described by Wells as a 'young physician'

†Dr Thomas Young, 1773–1829

'dry and, in general society, ungracious manners' and tendency to 'take offence where no offence was intended. Yet he had great kindness and warmth of heart mixed up with these less amiable qualities'. His circle of intimates, which was very small, included David Hume,

He was never married, but lived by himself with only a single maid-servant in a small house in Serjeants' Inn, Fleet Street, a house in which he died in the evening of 18 September 1817.

At his request his body was deposited in Lady Jersey's vault in St Bride's Church, Fleet Street.

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Recurrent erosion of the cornea

NICHOLAS BROWN AND ANTHONY BRON
From the Institute of Ophthalmology, Judd Street, London

In previous studies of superficial corneal disorders (Bron and Brown, 1971) and of superficial lines of the cornea (Brown and Bron, 1976), we were impressed by the frequency of recurrent erosion of the cornea. In this study we have set out to examine patients presenting with recurrent erosion of the cornea to establish the type and incidence of the superficial corneal disorders, and to compare this incidence with that in a control group of subjects. Some experience of management of these patients is also reported.

Material and methods

MATERIAL

Patients presenting at the Casualty Department at Moorfields Eye Hospital with suspected recurrent erosion of the cornea were referred by the casualty officers and examined by one of us. The patient was admitted to the study if the diagnostic criteria were satisfied. These criteria were:

1. A history of initial trauma or abrasion followed by a recurrence of pain with healing, followed by a clinical recurrence at the time of presentation and associated at some time with the clinical signs of recurrent erosion.
2. A typical clinical history of at least two attacks suggestive of recurrent erosion (pain on waking or being awakened, difficulty in opening the eye lid, watering, light sensitivity), without a history of trauma but associated with clinical signs of recurrent erosion at some time.

For each group, the clinical signs of recurrent erosion could include not only frank epithelial loss, but also focal epithelial oedema, epithelial bulla formation, and epithelial cyst formation in varying combinations. In this way, 80 patients were admitted to the study with ages ranging from 24 to 73 years.

The control group consisted of 200 patients aged between 20 and 85 years, who had attended clinics at Moorfields but were not complaining of any symptoms referrable to the cornea, and had no history of corneal disease.

METHODS

A proforma was completed for each patient; this contained a full clinical history (including details of the menstrual cycle and use of the contraceptive pill) and details of the examination of both eyes, including lids, tear films, corneae, and anterior chambers. The corneae were then re-examined after staining with fluorescein and with bengal rose. The corneal signs were recorded with the Zeiss photo slit lamp and with the macro camera (Brown, 1970) at 10× magnification.

Each patient was re-examined at least once after complete healing of the erosion and both corneae were inspected for superficial dystrophies. The ocular tensions were measured at this time.

Despite the traditional name for the disorder, it is recognized that frank epithelial loss is not required to establish the diagnosis and that focal epithelial oedema or bulla formation with or without a breach in the epithelium, and/or the presence of epithelial cysts, are in keeping with the diagnosis when associated with the typical clinical history. The patients were classed as having either macroform or microform recurrent erosion by the criteria of Chandler (1945). Microform recurrent erosion was recognized by intraepithelial microcysts with a minor break in the epithelium (Fig. 1). In macroform recurrent erosion, a large area of epithelium was separated from the cornea (Fig. 2).

TREATMENT AND FOLLOW-UP

The initial treatment was decided by the Casualty Officer and consisted of either chloramphenicol drops or chloramphenicol ointment with hyoscine 0·5 per cent drops, and padding for the eye. Patients with large bags of loose epithelium were treated initially by debridement, the loose corneal epithelium being carefully removed at the slit lamp with a Bard Parker no. 15 blade, using centripetal strokes to avoid stripping off an unnecessarily large area of epithelium. The eye was then treated with drops or ointment and padded as above.

Eyes which failed to heal on medical treatment and produced redundant loose epithelium were debrided as above. In those eyes which still failed to heal on this regime, the debridement was repeated and followed by carbolization with 100 per cent phenol applied at the slit lamp with a small stick to the dried cornea. Care was taken to avoid carbolizing the pupillary area of the cornea, but the phenol was otherwise applied to as much of the affected area as possible.

Once healing was complete the patients were given sodium chloride 5 per cent ointment to apply each evening immediately before going to bed. This treatment was continued for from 3 to 18 months. Treatment of longer duration was given in patients who found that

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Address for reprints: N. Brown, Institute of Ophthalmology, Judd Street, London WC1H 9QS

they suffered relapses if they omitted to apply their ointment.

Treatment was eventually withdrawn from all patients still attending at 18 months and the relapse rate was compared with that while on treatment.

Results

AGE AND SEX DISTRIBUTION (Table I)

The age and sex distribution of the patients is shown in Table I, together with the incidence of macroform and microform recurrent erosion; it is common for both forms to occur in the same individual at different times (31 per cent of patients). Bilateral recurrent erosion is relatively uncommon (10 per cent of patients).

CAUSES OF INITIAL ABRASION (Table II)

The initial abrasion was frequently spontaneous (40 per cent of patients) and the patient was unable to remember any trauma having preceded it. Of the identifiable causes (Table II), the most common was a scratch by a finger nail, scratches from a baby's finger being particularly prevalent among women. Among men, the causes were also related to their occupations, and metallic objects such as screwdrivers were described as causative. Two cases were seen after the removal of corneal foreign bodies. In the two hereditary cases the patients had no recollection of trauma.

The microform type was the most common in the spontaneous cases (Table II), whereas macroform and combined macroform and microform erosions were more commonly of traumatic origin. In the eight bilateral cases trauma was reported

Table I *Age and sex distribution of* 80 *patients**

Age group (years)	*No. of patients*
21–30	13
31–40	22
41–50	22
51–60	18
61+	5
At presentation (mean)	42
Percentage of women	48
men	52

Type of recurrent erosion	*No.*	*Percentage*
Macroform only	10	13
Microform only	45	56
Both types in same individual	25	31
Bilateral cases	8	10

*The youngest was 24, the eldest 73 years

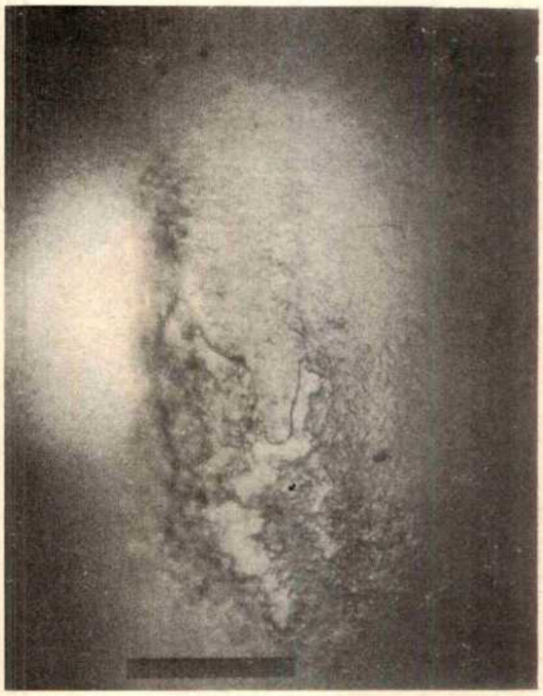

FIG. 1 *Microform recurrent erosion. Macrophotograph by retroillumination. Bar gauge* 500 μm

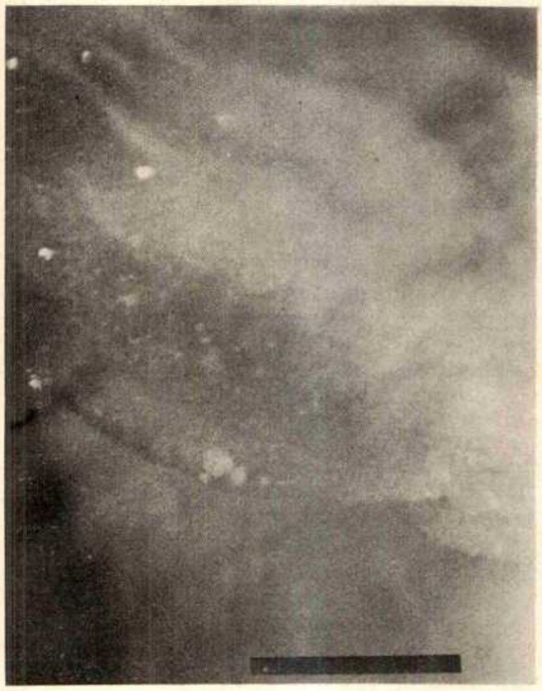

FIG. 2 *Macroform recurrent erosion. Stained with fluorescein to show intraepithelial microcysts. Bar gauge* 1000 μm

Table II *Causes of abrasion in 80 patients*

Abrasion	*No.*	*Percentage*
Spontaneous	32	40
Finger nail	18	22
Animal claw	3	4
Vegetable matter, for example, twig	12	15
Paper or card	7	9
Metallic object	5	6
Corneal foreign body	2	
Contact lens	1	

Relation of erosion type to trauma	*No.*	*Percentage of traumatic cases*	*No.*	*Percentage of spontaneous cases*
Macroform alone	8	10	2	3
Microform alone	20	25	25	31
Combined form	20	25	5	6

Table III *Recurrences in 80 patients*

Time of recurrence	*Percentage*
At about the time of waking	76
Before waking (awakened by pain)	30
After waking	40
Difficulty in opening the eye	10
At other times of the day	24
Precipitation	
Nil	86
Eye rubbing	10
Barbiturates	2·5
Menstruation	1

by only three, and in two of these patients, the trauma had been to one eye only.

FREQUENCY AND PRECIPITATION OF RECURRENCE (Table III)

The interval before the first recurrence after the initial abrasion varied from 2 days to 16 years, but it may be doubted whether this late recurrence was related to the initial abrasion after so long a time. The mean interval was 18 months, but this was weighted by a few very long durations, and 63 per cent occurred within 4 months.

Recurrences, both macro- and microform, occurred most commonly at around the time of waking (Table III). Some patients were able to give a clear history of being awakened by the pain and, in others, the pain occurred after waking. An interesting symptom was difficulty in opening the lids; some patients needed to use their fingers to open their eye, and this was commonly followed immediately by a recurrence.

Precipitating factors were sought in the patient's history, but none was elicited in 86 per cent. Eye rubbing was admitted as a cause in 10 per cent and the use of barbiturates was implicated in 3 per cent. These patients experienced recurrences whenever they resumed taking barbiturates.

Altogether 23 menstruating women were studied, and in only one of these was there a clear history of recurrences related to the time of onset of each menstruation.

The general health of the patients appeared to be unrelated; the only finding which was in any way consistent was that of a history of atopy in 5 per cent. A family history suggesting dominant inheritance of recurrent erosion was obtained in two patients (3 per cent).

The frequency of recurrence was very variable, ranging from a minor recurrence each morning to major recurrences separated by many months. The frequency of recurrence varied between patients and at different periods in the same individual.

The recurrences lasted from 1 to 4 hours in the microform condition, and from 1 to 21 days in the macroform condition, which included two cases in which the healing was delayed by a secondary bacterial infection.

SYMPTOMS (Table IV)

The symptoms of recurrence (Table IV) are largely as anticipated. Blurring of vision varied from absent or minimal in many eyes with microform erosion to severe in macroform erosions.

SIGNS

When the eyes were examined at the time of active erosion, a small epithelial break (Fig. 1) was seen

Table IV *Symptoms of recurrent erosion in 80 patients*

Symptoms	*Percentage of patients*
Pain	93
Severe pain	10
Blurring of vision	61
Watering	72
Photophobia	57
Redness	10

in microform erosion and a larger break, commonly with loose baggy epithelium around it, in macroform erosion (Fig. 2). The common site was central, just below the pupil. In both forms microcysts were present in the surrounding epithelium which usually stained well with fluorescein (Fig. 2). Some degree of epithelial and stromal oedema was common. The conjunctiva was injected and sometimes chemosed, especially in cases of macroform type. The anterior chamber was normally quiet, but sometimes showed a few cells in macroform cases.

In the healed state the eyelids and conjunctiva were unremarkable and an abnormal intraocular pressure was not found. Tear film thinning, demonstrated by the break-up of the fluorescein film, was found in 14 per cent. This was usually related to an area where the epithelium was uneven because of a superficial corneal dystrophy or epithelial cysts. However, the volume of tears did not appear to be abnormal and Schirmer's test gave results within the normal range.

SUPERFICIAL CORNEAL DYSTROPHIES
(Tables V, VI, and VII)

(The term superficial corneal dystrophy will be used for the group of changes occurring in the region of the corneal epithelium and defined below. Evidence for a genetic aetiology is currently small. See discussion.)

Superficial corneal dystrophies were a frequent finding (Table V) and commonly bilateral. The occurrence of the dystrophies was related to the age of the patient (Table VI). No patient seen in the present study was below the age of 30 years, but we have occasionally seen affected patients below this age. The frequency increases with age, reaching 78 per cent of patients in the 51 to 60 year age group.

The incidence of superficial corneal dystrophies in the patients is compared with that in the control group in Table IX. In the unilateral cases, the dystrophy was more frequently found in the unaffected eye than in the eye affected by recurrent corneal erosion, from which it may be deduced that the corneal erosion had been responsible for erasing clinical signs of the dystrophy.

The types of dystrophies which were found (Table V), were most commonly the various superficial corneal lines, which are listed separately in Table VII. Bleb dystrophy was also common, less commonly found was the more pronounced lacunar dystrophy of Bietti (1965) which we regard as synonymous with the 'map change' of Guerry (1965).

The individual superficial corneal lines have been described in detail (Brown and Bron, 1976). The most common type is the now familiar 'fingerprint line' (Fig. 3) first described by Guerry (1950). These are fine refractile lines which are best seen by retroillumination. They are arranged in a near parallel whorl-like pattern, which gives them their resemblance to a fingerprint. Tear film thinning is commonly seen over the line. Two other fine lines which have the same retroillumination appearance as the fingerprint line, but differ in arrangement, are the superficial ring lines and superficial corneal crazing. The superficial ring lines form complete rings and the superficial

Table V *Incidence of superficial corneal dystrophies (including all types of lines)*

Dystrophy	*Percentage**
All patients with superficial dystrophy or lines	59
Bilateral	66
In affected eye only	8
In unaffected eye	12
Fine superficial lines	46
Bleb dystrophy	28
Bietti's lacunar dystrophy (map dystrophy)	5

*Of 80 patients

Table VI *Age distribution of patients with superficial corneal dystrophies (excluding demarcation lines)*

Age group (years)	*Patients*		*Percentage of age group*
	No.	*With dystrophy*	
21–30	13	0	0
31–40	22	9	41
41–50	22	15	68
51–60	18	14	78
61+	5	3	60

Table VII *Incidence of fine superficial corneal lines*

Corneal lines	*No.*	*Percentage**
Patients affected	37	46
Fingerprint lines	21	26
Demarcation lines	17	21
Superficial ring lines	1	—
Superficial corneal crazing	2	—
Mare's-tail lines	1	—
Tram lines	2	—
Bleb dystrophy and fingerprint lines in association	14	17

*Of 80 patients

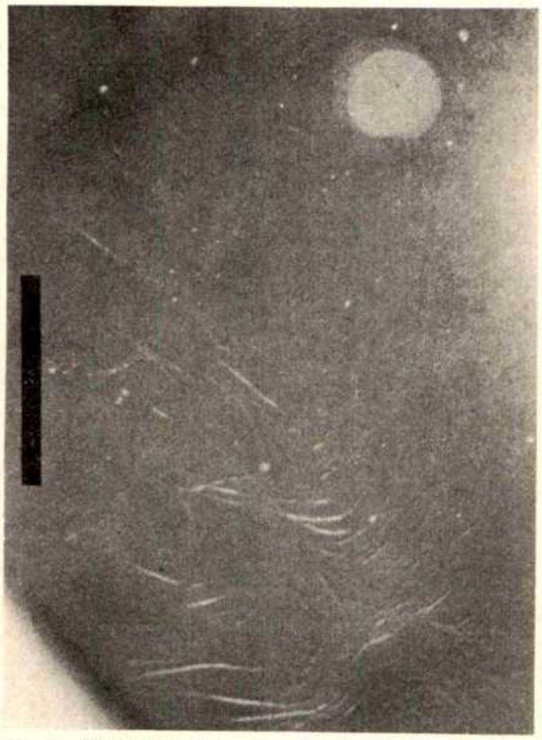

FIG. 3 *Fingerprint lines. Seen by retroillumination of fundus. Bar gauge* 1000 μm

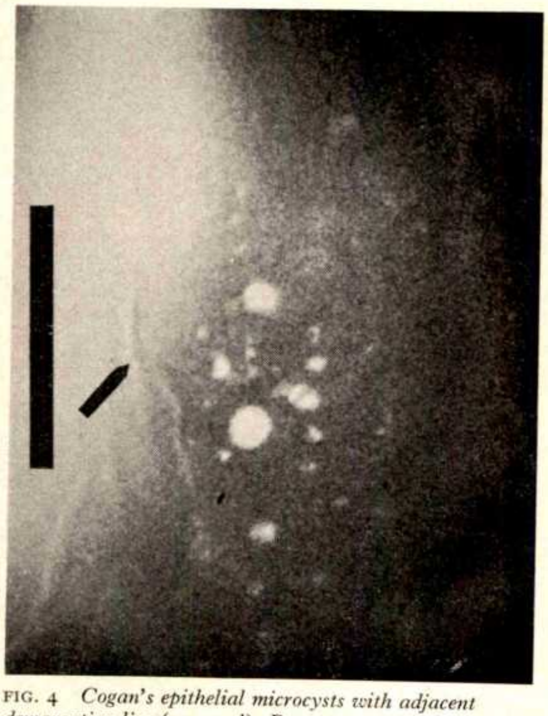

FIG. 4 *Cogan's epithelial microcysts with adjacent demarcation line* (arrowed). *Bar gauge* 500 μm

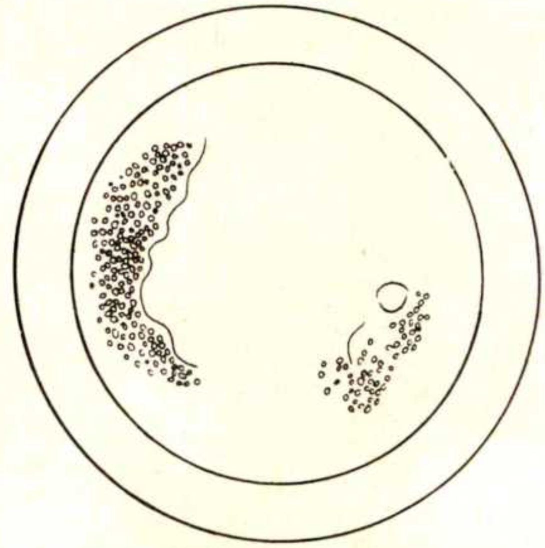

FIG. 5 *Demarcation lines marking limit of area of bleb dystrophy*

corneal crazing is found near the limbus and differs from the fingerprint line in having a branched pattern. Neither of these lines was common, but since each probably represents variants of the fingerprint line, its presence is considered to be related to recurrent erosion.

'Demarcation lines' (Fig. 4) have a superficial resemblance to fingerprint lines and are often found in the same eye where they separate areas affected by fingerprint lines, or by bleb dystrophy, from clear areas (Fig. 5). These lines often form complete rings of about 5 mm in diameter. They occur in eyes which have had recurrent erosion and are not seen in the fellow eye unless that too has been affected by erosion.

'Mare's-tail lines' (Fig. 6) are recognizably different from fingerprint lines, being seen best by focal illumination. These lines are bunched together in places and spread out in others; they show branching and crossing, which do not occur in fingerprint lines. They appear to be more superficial than the other lines and have a significant effect in thinning the tear film. Although only one patient is reported with mare's-tail lines in this series, we have seen them in other patients with recurrent erosion and in association with Bietti's lacunar dystrophy which is also related to recurrent erosion.

The remaining lines are 'tram lines', described by Brown and Bron (1976). These rare lines run a long, straight, nearly vertical course, and have refractile edges with the appearance of parallel tram lines. They were found in two patients in this series and in none of the controls. We are

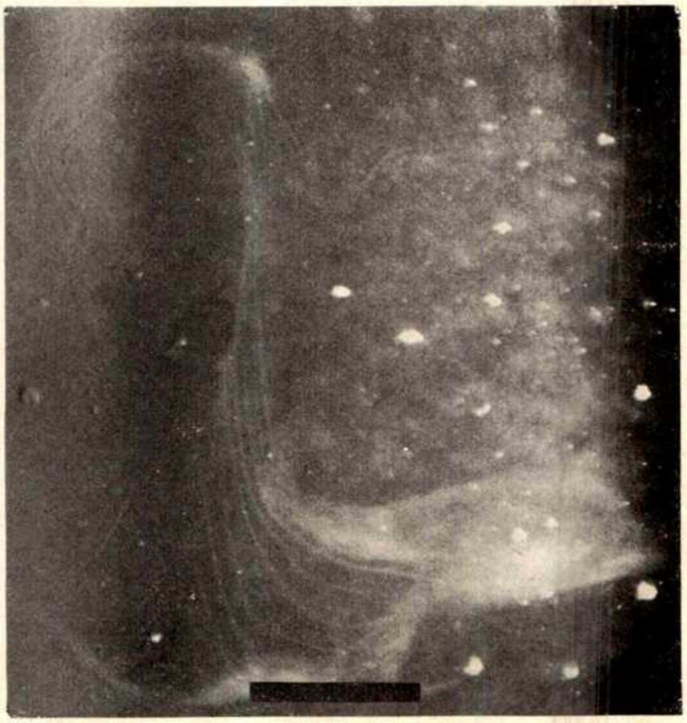

FIG. 6 *Mare's-tail lines by focal illumination. Bar gauge 500 µm*

unable to say whether their presence is related to recurrent erosion.

Dystrophic changes consisting of fine superficial blebs (Bron and Brown, 1971) were found in 28 per cent of patients. The blebs are seen only by retroillumination (Fig. 7) when they have the appearance of pebbled glass. They are subepithelial and do not affect the tear film. The blebs occurred in groups, sometimes covering large areas of the cornea, and were sometimes arranged in a characteristic hexagonal net pattern (Bron and Jones, 1969). Blebs were often absent from the region just below the pupil in eyes which had suffered recurrent erosion and in these eyes their limit was characteristically defined by a demarcation line (Fig. 5).

A less common finding (in 5 per cent of the patients and in none of the controls) was the superficial corneal dystrophy described by Bietti (1965) as lacunar dystrophy of Bowman's membrane (Fig. 8), in which clear lacunae up to 2 mm in diameter are seen on the surface of Bowman's membrane. The areas between the lacunae are opalescent and the edges of the lacunae are defined by a denser white line which may have a rolled appearance in focal illumination. The irregular pattern produced by the lacunae gives a map-like appearance, so that it is probably the same condition as that described by Guerry (1965) and thought by him to be a component of the epithelial microcystic disorder described by Cogan, Donaldson, Kuwabara, and Marshall (1964). Numerous other workers have since observed these map-like changes (Wolter and Fralick, 1966; Levitt, 1971; Trobe and Laibson, 1972; Luxenberg, Friedland, and Holder, 1975).

MICROCYSTS (Table VIII)

Intraepithelial microcysts (Fig. 9) were a common finding in healed eyes, being present in 59 per cent of the patients (Table VIII), but they were seen in only 1·5 per cent of the controls (Table X). They occurred in conjunction with other recognizable dystrophies, but were the only recognizable corneal signs in 21 per cent. This left only 11 per cent of patients in whom no signs, either cysts or dystro-

Table VIII *Microcysts*

Microcysts	*Percentage*
Patients affected (total)	59
Erosion-affected eye only	49
Unaffected eye	24
Cogan's microcysts	6
Microcysts as only recognizable signs	21
Patients with neither dystrophy nor microcysts	11

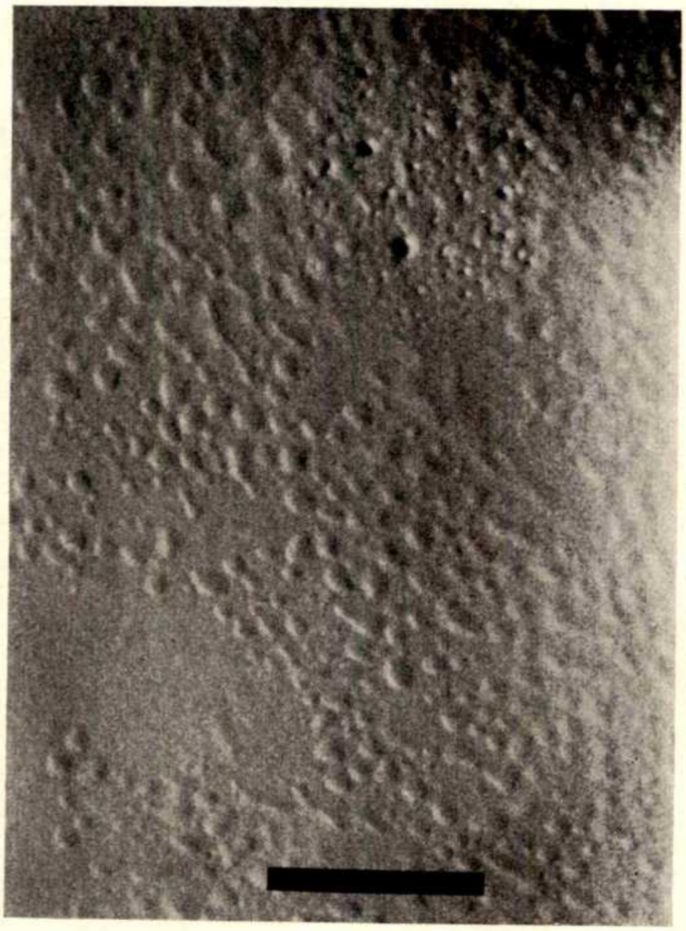

FIG. 7 *Bleb dystrophy by retroillumination of fundus. Bar gauge* 500 μm

phies, were visible in the healed state. In most patients a retrospective diagnosis of recurrent erosion could be made with confidence when examining the patient in the healed state. Clinical symptoms, however, were always associated with clinical signs.

The microcysts were seen best by retroillumination, but sometimes contained opaque matter which made them visible by focal illumination. (This was most marked in those opaque white cysts having the appearance of those described by Cogan and others, 1964.) The microcysts, measured from the corneal macrophotographs, varied from 20 μm to 74 μm in diameter. The more superficial cysts, which sometimes showed a centrally umbilicated appearance, commonly stained with fluorescein, and those which did not stain showed as dark spots in the fluorescein, containing tear film. It was noticed that the cysts which were first seen after healing of an erosion showed the same distribution of light within them as that of the background when viewed by marginal retroillumination, which has been taken to imply a lower refractive index than that of the surrounding epithelium (Brown, 1971). After a month or more of treatment the cysts tended to be smaller and more discrete and in many eyes had disappeared. The remaining cysts sometimes changed their appearance as seen by retroillumination so that they now reversed the illumination compared with that of the background, implying a refractive index higher than that of the surrounding epithelium. The appearance was now like that of small oil droplets.

THE CONTROL GROUP (Table IX)

The findings in the controls are presented in Table IX. A low incidence of superficial dystrophies of the fingerprint line and bleb type and a few microcysts were found. In none of the controls was there any history of recurrent erosion, nor were there any symptoms referrable to the cornea.

Table IX *Incidence of superficial corneal dystrophies in 200 control eyes*

Superficial corneal dystrophies	*Percentage*
Fingerprint lines	1·5
Microcysts	1·5
Blebs (including net patterns)	2·0

FOLLOW-UP AND RESPONSE TO TREATMENT (Table X).

Altogether 70 patients attended for follow-up from 1 to 48 months (mean 16 months).

Healing occurred after the recurrent erosion with which the patient had presented, in a few hours in minor microform and up to 3 weeks in severe macroform erosions. In two eyes, taking 3 weeks to heal, the healing had been delayed by corneal infiltration and oedema due to secondary bacterial infection. A healing time of 1 to 2 days was normal for the macroform erosions. The initial treatment given by the Casualty Officer was chloramphenicol drops or ointment and it did not appear to matter which of these was given. Debridement was performed as an initial treatment in 12 eyes which had large bags of loose epithelium. In each, this was followed by healing in 2 to 4 days (mean 3·1 days), and no cases of delayed healing occurred in these patients. Debridement was also carried out in four eyes showing lack of spontaneous healing with medical treatment during which a loose bag of epithelium developed. After

Table X *Response to prophylactic treatment for 3–18 months (mean 10 months)*

Treatment	*No. of patients*	*Percentage**
NaCl 5 per cent ointment	60	60
Symptom-free	32	53
Improved	16	27
Not improved	2	3
Inadequate follow-up	5	8
Ointment rejected for stinging	5	8
Recurrences on treatment:		
Microform	8	14
Macroform	8	14
Effect of stopping treatment for 3 months†		
Treatment stopped in	32	
but 3 persisted against advice		
Therefore total in group	29	
Remaining symptom-free	5	17
Unchanged	5	17
Deteriorated	17	59
Recurrences off treatment:		
Microform	19	65
Macroform	3	10

*Of 60 patients †Of 29 patients

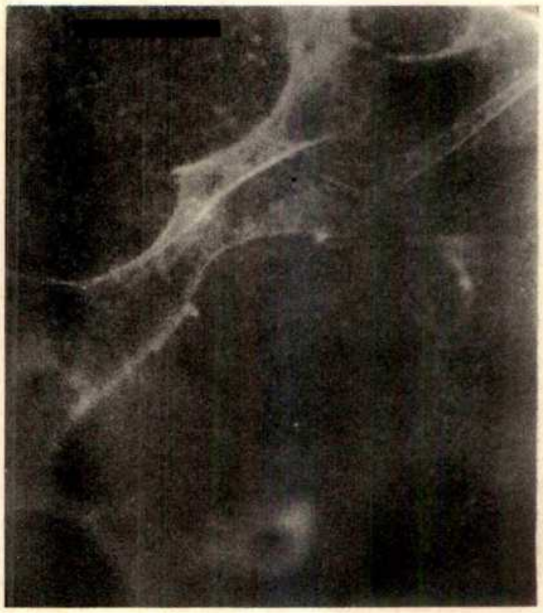

FIG. 8 *Bietti's lacunar dystrophy (map dystrophy). Bar gauge 500 μm*

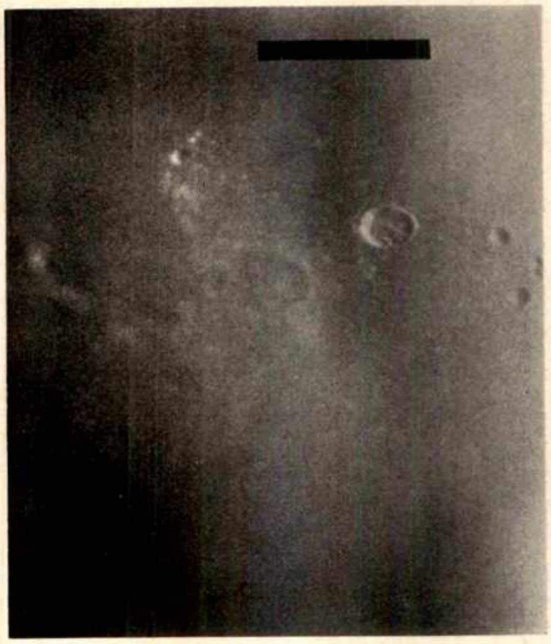

FIG. 9 *Intraepithelial microcysts. Late stage of treatment showing reversal of marginal retroillumination. Bar gauge 500 μm*

debridement, the epithelium was able to grow smoothly across the stroma. The incidence of recurrence after debridement did not differ from that in eyes which had received medical treatment alone. In one eye a deliberate attempt was made to scarify the surface of Bowman's membrane at debridement. No recurrence occurred in this eye, but the debridement left a faint superficial nebula.

Carbolization was performed after debridement in seven eyes and was followed by healing in 2 to 4 days. There was a single recurrence of a macroform erosion in two eyes and there were several recurrences of microform erosions in one eye which had been carbolized. Carbolization appears to be beneficial in reducing recurrence, but the number of eyes so treated was too small for the results to be significant.

Once healing was complete, 60 patients were given sodium chloride 5 per cent ointment to apply each evening immediately before going to bed. The result of this treatment was assessed after 3 months (Table X). Most patients were improved or even symptom free, but in some there were recurrences. The ointment was well tolerated by most patients, but 8 per cent found that it stung and stopped using it.

The effect of deliberately stopping the sodium chloride ointment was tested in 32 patients (Table X) after treatment for 3 to 18 months. The patients' symptoms tended to deteriorate, particularly with an increased incidence of recurrence of microform erosions. Thus three patients persisted in using the ointment against advice. It appeared that treatment could be more successfully withdrawn after a long period (12 months or more), and it was considered proper to withdraw treatment from all patients once they were able to remain comfortable without the ointment. Those in whom symptoms recurred resumed the use of the ointment.

Discussion

CLINICAL FEATURES

Recurrent erosion of the cornea has often been described, and a review of the early literature was well presented by Chandler (1945). The appearance of the active erosion has been fully documented and Chandler was able to divide the erosions, both symptomatically and by their appearance, into macroform and microform. This appears to be a useful classification, but it is now seen that the two different forms can occur in the same corneae at different times, and it is considered that there is no sharp distinction between the two disorders. Chandler found that macroform erosions were more commonly the result of trauma than microform erosions, which is confirmed by our observations.

The existence of bilateral cases was recognized by Chandler but has been considered rare, so that Flynn and Esterly (1966) thought it worthwhile to report a single case. The 10 per cent incidence of bilateral cases in our series is rather higher than that suggested in the literature.

An inherited form of recurrent erosion has been recognized since Franceschetti (1928) reported a family with a dominant inheritance. It would appear from our experience and that of other authors that a family history is uncommon. Two of our patients had a family history, but in neither case was there sufficient information to be certain of the pattern of inheritance.

The relationship of the time of the recurrence to the time of waking is interesting. We are in agreement with Chandler (1945) that the recurrence may occur before or after waking, although Szili (1900) maintained that patients always awoke first. In our patients who awakened first, difficulty in eyelid opening was commonly experienced, which suggests that there was an adhesion between the corneal epithelium and the eyelids. It is obscure why this should occur even if the epithelium is first lifted from the cornea. Drying of the tear film with incomplete lid closure in sleep has been suggested to account for this (Sturrock, 1975, personal communication). However, most authors take the opposite view and consider that increase in fluid in the cornea which lifts off the epithelium causes the recurrence. Thus Chandler (1945) and Theodore (1964) considered that an endothelial defect might be important in allowing fluid entry into the stroma; and Valle (1967) reported a family showing dominant inheritance of recurrent erosion in which one member had Fuchs's endothelial dystrophy which Valle considered to be significant. Cogan (1941) demonstrated the hypotonicity of tears during the night which he considered relevant in allowing fluid entry into the epithelium, and Thygeson (1959) considered that persistent epithelial oedema was a significant factor.

A rational approach to prophylaxis is therefore to use a lubricating agent at bedtime to prevent adhesion between the corneal epithelium and the lid, and an agent to produce corneal desiccation. The use of ointments as lubricants is traditionally accepted and methyl cellulose drops have been recommended by Guyard and Perdriel (1961) and by Theodore (1964). Theodore also recommended lowering intraocular pressure by acetazolamide. A combined lubricant and desiccating agent is convenient; Chandler (1945) and Thygeson (1959) used 10 per cent boric ointment, and Goldman, Dohlman, and Kravitz (1969), and Trobe and Laibson (1972), like ourselves, used 5 per cent sodium chloride ointment.

The existence of superficial corneal dystrophies in relation to recurrent erosion was probably first recognized by Vogt (1930) who observed spots and fine glassy lines which appear in his illustration to be the same as those now called fingerprint lines. Brückner (1950) stated that no slit-lamp abnormality was to be seen in healed recurrent erosion, but he was able to demonstrate irregularity of the cornea with the Fisher reflectographic technique which is capable of demonstrating such fine abnormalities as the anterior corneal mosaic (Bron, 1968), also demonstrable by the proper use of retroillumination.

Several other authors, as reviewed by Chandler (1945), have described white or grey dots in corneae with healed recurrent erosions and these dots may now be described as microcysts. Microcysts may be relatively clear, with a low content of cellular debris, and variable in size; they are sometimes fused together and often take up fluorescein stain. The microcysts of Cogan's microcystic disorder are more often densely opaque and discrete; they fail to take up stain and may reach a large size (Bron and Tripathi, 1973). Although such cysts may occur together in the same cornea, their morphogenesis may be different. Like Cogan, Kuwabara, Donaldson, and Collins (1974), we believe that the special features of the Cogan type of cyst relate to their sequestration behind anomalous intraepithelial basement membrane sheets (Bron and Tripathi, in preparation). Cogan's microcystic dystrophy has in the past been regarded as benign and responsible at most for minor irritative symptoms (Cogan and others, 1964; Guerry, 1965; Levitt, 1971; Bron and Tripathi, 1973; Luxenberg and others, 1975). Attention has been drawn by Trobe and Laibson (1972) to the association of these cysts with map dystrophy (which we regard as identical to the lacunar dystrophy of Bietti (1965)) and with fingerprint lines and recurrent corneal erosion. Brodrick, Dark, and Peace (1974) confirmed the relationship between Cogan's microcystic dystrophy, fingerprint lines, and recurrent corneal erosion. In the present study cysts of the Cogan type and map-like dystrophy are found, but their incidence is low.

Proper attention has only recently been given to the relationship between the superficial dystrophies of the fingerprint line, bleb, and net type and recurrent corneal erosion; in fact Guerry (1950), in his original description of fingerprint lines, considered them to be of no pathological significance, but a relationship between fingerprint lines and recurrent erosion has been reported by Kaufman and Clower (1966), Bron and Brown (1971), Trobe and Laibson (1972), Brodrick and others (1974), and Brown and Bron (1976), and between bleb and net patterns and recurrent erosion (Bron and Brown, 1971).

It appears that the various superficial corneal disorders which are associated with recurrent corneal erosion are not discrete entities but represent a spectrum of visible signs with a common pathological background. Many of our patients showed several different forms of disorder in the same or fellow eye and this relationship has been commented upon previously; Guerry (1965) and Levitt (1971) reported the relationship between Cogan's microcystic and map-like changes, Bron and Brown (1971) reported the association of fingerprint lines and bleb and net patterns together, and their relationship with recurrent erosion, and Trobe and Laibson (1972) reported the relationship between Cogan's microcystic dystrophy, map-like dystrophy and fingerprint lines, and recurrent erosion.

Most corneal abrasions heal satisfactorily and are not followed by recurrent erosion. Jackson (1960) saw one recurrent erosion in 150 abrasions and Guyard and Perdriel (1961) saw no recurrences in 40 abrasions.

It appears that recurrent erosion follows in a cornea which is already abnormal. The high incidence of superficial corneal dystrophies in our patients (Table V) as compared to controls (Table IX) supports this suggestion. That the superficial dystrophies are the precursor of the erosion and not the result of it, is demonstrated by their higher incidence and greater extent in the asymptomatic eye (Table V). The recurrent erosion appears to erase the dystrophic changes so that they may be absent or only minimally present in the healed cornea. The dystrophic change has also been removed by deliberate debridement as observed for fingerprint lines by Guerry (1950), and for Cogan's microcystic dystrophy by Wolter and Fralick (1966) and Cogan and others (1964, 1974). This would occur if the defective basement membrane (see below) was also shed with the lost epithelium.

In our earlier study (Bron and Brown, 1971), 40 patients ranging in age from 39 to 41 years were found to exhibit superficial corneal changes of the fingerprint, bleb, and net pattern and the changes were bilateral in 73 per cent, suggesting a dystrophic or degenerative aetiology. Symptoms of recurrent erosion were seen in 38 per cent of patients. In the present study of 80 patients with recurrent erosion syndrome, the incidence of superficial corneal changes (fingerprints, blebs, nets, and maps) was 59 per cent compared to 3·5 per cent in the control group (lines and blebs). (Cysts are excluded from the comparison because they may at times be a non-specific expression of the presence of epithelial oedema. Data are available in Tables VIII and IX.) This strongly supports the contention that the superficial corneal changes under discussion are responsible for defective epithelial adherence and render patients vulnerable to recurrent erosion.

It appears that the patients studied by us in the past (Bron and Brown, 1971) and in the present study are substantially the same group as that studied by Trobe and Laibson (1972). Differences relate to the low incidence of map change and Cogan's cyst change in our studies and to the absence of net and bleb changes in the series studied by Trobe and Laibson. These differences may relate in part to matters of definition, since we attempted to distinguish on biomicroscopic grounds cysts of the Cogan type from other microcysts associated with recurrent erosion (Bron and Tripathi, 1973), and in part to methods of examination. It is important to emphasize the need for careful examination of the cornea by retroillumination, using first the iris and then the red reflex of the fundus with the pupil dilated, in order not to miss the finest dystrophic changes.

It seems likely that a common histopathological factor in all these disorders is the anomalous production of basement membrane material and other connective tissue sheets both within and sometimes deep to the corneal epithelium. This has been observed both in the absence of clinical map-like changes (Cogan and others, 1964, 1974), and in their presence (Guerry, 1965; King and Geeraets, 1972; Tripathi and Bron, 1973; Rodrigues, Fine, Laibson, and Zimmerman, 1974; Fogle, Kenyon, Stark, and Green, 1975; Dark, Brodrick, and Peace, 1973), and Brodrick and others (1974), demonstrated the presence of a fibrillo-granular material with intra- and subepithelial extension in a patient with fingerprint lines. The histopathology of bleb and net patterns is not yet known.

The relevance of basement membrane abnormalities to recurrent erosion has been clarified in recent years. Khoudadoust, Silverstein, Kenyon, and Dowling (1968) experimentally showed the importance of the basement membrane and of the hemidesmosomes of the basal epithelium to epithelial adherence. Poor epithelial adherence is implied by the erosion itself and can be demonstrated by manipulating a contact lens on the healed cornea of these patients (Lowe, 1964, 1970). A defective basement membrane was demonstrated in traumatic recurrent erosion by Goldman and others (1969), and in spontaneous recurrent erosion by Tripathi and Bron (1972), who also noted an absence of hemidesmosomes in relation to affected basal cells. Kenyon (1969) suggested that deficiencies in the formation of basement membrane, hemidesmosomes, and attachment fibrils account for the erosive events encountered in Reis-Bückler's dystrophy, Cogan's microcystic dystrophy, and non-traumatic recurrent erosion (Fogle and others, 1975). Presumably a similar mechanism is involved in metaherpetic keratitis (Kaufman, 1964).

It would appear that the biomicroscopic appearance of fingerprint lines, of map changes, and probably of the net and bleb patterns relate to the location, amounts, and optical properties of anomalous basement membrane and other connective tissue material situated in the affected epithelium, and that recurrent erosion episodes are related partly to the presence of subepithelial connective tissue sheets and to a disturbance of the epithelial adhesion mechanism.

RESPONSE TO TREATMENT

In the initial treatment it would appear to make no difference whether the antibiotic is given as drops or an ointment, which accords with the experimental work of Hanna, Fraunfelder, Cable, and Hardberger (1973). The complication of entrapment of ointment beneath the epithelium (Fraunfelder, Hanna, Cable, and Hardberger, 1973) was not seen. However, it was noticed that the refractile appearance of microcysts as seen on retroillumination could change so that they came to resemble oil droplets.

Simple debridement, without scarification or carbolization of the surface of Bowman's membrane, appears to be beneficial in assisting healing of a macroform erosion, but not in preventing recurrence. This is not surprising since the problem appears to be one of epithelial adherence rather than of epithelial resurfacing. Some form of physical or chemical injury to the cornea has commonly been recommended. Chemical cautery has frequently been advocated (Chandler, 1945), and our own experience with carbolization in a small number of patients would appear to support this. However, carbolization does leave a faint superficial nebula, and is best avoided except for highly intractable recurrent erosions. Debridement with deliberate scarification of Bowman's membrane has been recommended (Kaufman and Clower, 1966; Trobe and Laibson, 1972) and is probably useful in preventing recurrence, as in the only case so treated by us. However, this also leaves a superficial scarring.

Successful prophylactic treatment with hypertonic agents has been described by Chandler (1945), Thygeson (1959), Goldman and others (1969), and Trobe and Laibson (1972). The hypertonic agent which we used, sodium chloride ointment 5 per cent, was shown to be effective in dehydrating the human cornea by Luxenberg and Green (1971) who obtained a reduction of 20 per cent in the thickness of oedematous corneae. The sodium chloride ointment was well tolerated by the patients and appears to have been effective in preventing recurrence, as witnessed by the increased incidence of recurrence once it had been withdrawn (Table IX). The reduction in size and the increase in refractility of the microcysts with their eventual disappearance in some eyes suggests desiccation.

Patients could be successfully withdrawn from treatment, particularly after long periods, so that it would appear that the use of the ointment is curative in the long run, or that recurrent erosion is a self-limiting disorder. The ointment is a logical choice (as discussed above), but we cannot be certain at present whether the lubricant or desiccant properties are the more important. A future trial against a simple lubricant ointment should be informative.

Conclusions

Recurrent erosions occur in corneae with poor adhesion between the epithelium and Bowman's membrane, and defective basement membrane complexes are implicated. The defect is commonly present in the cornea before the initial trauma as witnessed by the high incidence of superficial corneal dystrophies.

The examination of the cornea in the healed state commonly reveals a superficial dystrophy, or the presence of microcysts. The diagnosis of recurrent erosion can thus be made on slit-lamp examination in most healed cases and less reliance need be placed on the verbal history alone.

Fluid, collecting in or beneath the epithelium during the night, with resultant lifting of the epithelium and adherence of the epithelium to the tarsal conjunctiva are two possible factors leading to recurrence.

In the initial treatment it does not matter whether drops or ointment are used. Debridement of loose epithelium assists healing and resolves pain sooner, but does nothing to prevent recurrences. Recurrence is best prevented with a lubricant and desiccant substance (sodium chloride 5 per cent ointment) applied at bedtime. This can be discontinued after several months once the patient remains symptom free on withdrawal. No precise period for prophylactic treatment can be given and it must be adjusted for the individual patient. In eyes which continue to be severely affected by recurrence, in spite of prophylactic treatment, epithelial adhesion can be improved by carbolization or debridement with scarification, but these procedures may cause scarring.

Summary

Altogether, 80 patients aged between 24 and 73 years with recurrent erosion of the cornea have been studied and compared with a control group of 200. The patients' erosions were divisible into macroform and microform types. The macroform occurred in 10 per cent, the microform in 56 per cent, and both types in the same patients in 31 per cent. The macroform was more commonly related to trauma than the microform. However, many (40 per cent) were spontaneous in origin. The most common cause of the initial trauma was a finger nail.

The recurrences occurred at around the time of waking, either just before or just after. Difficulty in opening the eye occurred in 10 per cent. There was little evidence of precipitating factors, but eye rubbing was admitted by 10 per cent and barbiturates were implicated in 3 per cent.

The corneae were examined in the healed state, when a high incidence (59 per cent) were found to have superficial corneal dystrophies of the fingerprint lines, bleb, and Bietti's lacunar (map-like) types. These are considered individually, particular attention being paid to the distinctions between the various types of line resembling the fingerprint line. Epithelial microcysts were also a common finding (59 per cent) and were sometimes of the Cogan type. In only 11 per cent of patients were there no corneal signs in the healed state. The need for careful examination of the cornea by retro-illumination, using both the iris and the fundus, is stressed. The control group, in contrast, showed a very low incidence of dystrophies and cysts.

Treatment was given initially with either drops or ointment and no differences in healing were found. Debridement was performed in 12 eyes as an initial treatment and also in four eyes which were not healing on medical treatment. Debridement assisted healing, but did not prevent recurrence. One eye was treated with debridement and scarification and seven with carbolization. These procedures appeared to reduce the recurrence rate.

Sodium chloride ointment 5 per cent was found useful as a prophylactic taken at bedtime, and the recurrence rate increased when it was withdrawn.

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Nocturnal lagophthalmos and recurrent erosion

G. D. STURROCK
From the Casualty Department, Moorfields Eye Hospital, London

Corneal exposure due to incomplete lid closure is a widely recognized complication of conditions such as facial palsy, lid deformity, proptosis, and coma. It is less well known that corneal exposure can occur during sleep in subjects who have normal voluntary lid closure. This diagnosis was made when patients presented with the characteristic history of ocular pain or discomfort occurring after sleep, associated with corneal epithelial lesions in the interpalpebral zone.

Incidence and presentation

A total of 102 patients believed to have suffered corneal exposure during sleep were collected over a two-year period. Sixty-eight cases were examined personally and details of those remaining were provided by colleagues working in the same department.

The ages of the patients ranged from 17 to 82 years (average 42). Attacks had started at the age of 13 years in one patient, but for the whole series the incidence was highest in the third decade and slowly declined with increasing age.

Patients typically presented early in the day within a few hours of waking with their symptoms. The symptoms consisted of soreness, pricking discomfort or sharp pain in one eye, often associated with watering and sometimes blurred vision. Some patients had awoken during the night with pain in one eye. Symptoms were most pronounced immediately after their onset and tended to improve spontaneously during the course of the day. The appearance of symptoms in both eyes together was uncommon, and in the eight patients in whom this occurred, symptoms were always more marked in one eye than the other.

PREVIOUS ATTACKS

The number and pattern of attacks experienced by different patients varied. In 53 patients the presenting episode was their first and only attack, while in 18 there was a history of one or two previous attacks. Thirty-one patients had experienced multiple attacks during a period varying from months to as long as 16 years in one case. A few patients in this last group gave a history of attacks occurring on several mornings in succession.

ROLE OF ALCOHOL

The only factor of possible aetiological significance revealed by history was the taking of alcohol. Fifty-two patients admitted to having drunk alcohol during the previous evening, but in 19 the amount of alcohol involved was small. Twelve patients were calculated to have consumed the equivalent of between 50 and 100 ml pure alcohol, and 11 patients had taken between 100 and 200 ml alcohol. Another 10 patients stated that they had been drinking heavily or had drunk more than usual. An association between alcohol and nocturnal lagophthalmos was recognized by four patients, all with a history of multiple attacks.

Family history

There was a family history of sleeping with the eyes open in five patients, representing four separate families.

A 29-year-old woman had had persistent symptoms of nocturnal lagophthalmos for seven years, affecting mainly the left eye. Her brother had seen her sleeping with this eye partly open, and taping shut the lids at night gave relief from her symptoms. While in hospital for investigation three years ago she had been seen to sleep with the left eye partly open. Next morning a small area of punctate epithelial keratopathy had been visible in the interpalpebral zone of the left cornea. A neurological examination had been normal.

The 24-year-old brother of this patient attended the casualty department recently with the symptoms and signs of nocturnal lagophthalmos. He had drunk the equivalent of 110 ml alcohol the previous evening and awoken the next morning with a sore right eye. There was no history of previous attacks.

A 31-year-old man, in whom symptoms of nocturnal lagophthalmos had occurred intermittently for 1½ years, was seen after waking at 4.0 am with a sharp feeling in the right eye. Examination revealed corneal

Requests for reprints: G. D. Sturrock, Moorfields Eye Hospital, City Road, London EC1V 2PD

epithelial microcysts in the interpalpebral zone. The patient and his three daughters were all known to sleep with one or both eyes open at times.

A 42-year-old man gave a history of waking in the night with sore eyes for 15 years. Attacks occurred several times a year, on two or three nights in succession. He had attended the hospital frequently and the records for each visit showed punctate staining of both lower corneae. The patient, his father, his two sisters, and his son and daughter were all known to sleep with their eyes partly open.

A 54-year-old woman attended the hospital on two occasions in the past year with nocturnal lagophthalmos of first the left and then the right eye. She had been observed by her daughter to sleep with one eye open The patient's mother and two aunts were also known to sleep with their eyes open.

In addition to these patients with a family history, a further six patients had been told that they tended to sleep with their eyes open. Thus a total of 11 patients who attended with nocturnal lagophthalmos had been observed on one or more occasions to sleep with one or both eyes partly open. It is noteworthy that in many of these patients, and in particular the relatives of those with a family history, failure to close the eyes during sleep was not necessarily followed by symptoms. Whether or not corneal exposure occurs must depend upon the presence or absence of Bell's phenomenon (see below).

DESCRIPTION

As anticipated from the history, examination revealed involvement of only one eye in most cases, although bilateral corneal changes were seen on at least one occasion in 18 patients.

There was usually mild to moderate hyperaemia of the affected eye, but some eyes were not injected at all. However, the most important diagnostic finding was an area of epithelial disturbance located in the interpalpebral zone of the cornea. The lesions, which could easily be overlooked without the aid of a biomicroscope, consisted of punctate epithelial keratopathy (PEK) combined with epithelial microcysts. The PEK lesions were visible by focal illumination as greyish flecks and stippling which stained well with rose bengal but poorly, or not at all, with 2 per cent fluorescein dye. The epithelial microcysts were visible only by retroillumination and did not take up stain. The proportion of PEK to microcysts varied in different patients and some lesions consisted mostly of PEK while in others microcysts predominated.

Basically the epithelial disturbance took the form of a horizontal band, in some cases this was patchy and incomplete, running across the lower cornea (Figs 1, 2). The width of this band varied in different patients from a narrow line of less than ½ mm wide to a broad strip 4 or 5 mm wide. Sometimes, instead of a single band of epithelial lesions there were two horizontal lines. In some patients, examination of the apparently uninvolved eye revealed a few groups of microcysts situated below the centre of the cornea. Extension of rose bengal staining on to the adjacent bulbar conjunctiva was uncommon even in cases in which a wide and well-defined corneal band ran from limbus to limbus.

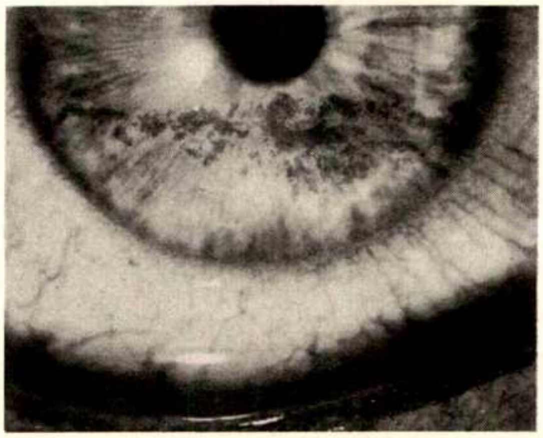

FIG. 1 *Area of partial thickness epithelial loss in centre of a band of rose bengal staining. Patient awoke with a sore eye after drinking the equivalent of 180 ml alcohol the previous evening*

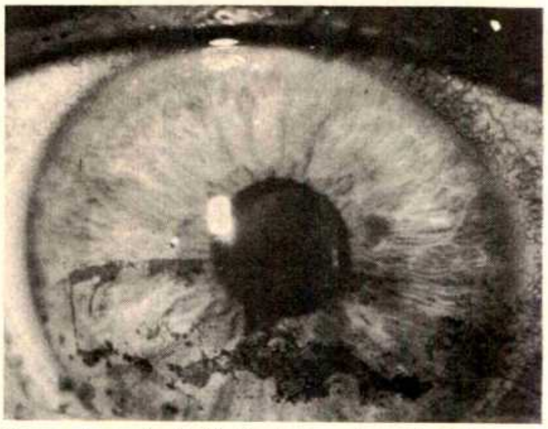

FIG. 2 *Irregular double band of rose bengal staining. Slightly curved upper border of lesion conforms to shape of upper lid margin*

In three patients a discrete grey faceted lesion was seen in the centre of a band of scattered PEK lying in the interpalpebral zone (Fig. 1). The central lesion stained strongly with 2 per cent fluorescein as well as with rose bengal dye and was thought to represent partial thickness epithelial loss.

Two other patients in whom nocturnal lagophthalmos was diagnosed presented on a different occasion with an area of complete epithelial loss (macroform recurrent erosion).

A 20-year-old man who was seen after waking with a sore right eye gave a history of a similar episode one year previously. Examination showed two horizontal strips of rose bengal staining across the lower cornea. After treatment with chloramphenicol ointment and a pad the eye was symptom-free next day and the cornea no longer stained. Four months later he again awoke with a painful right eye and was found to have an oval area of epithelial loss below the corneal centre. The eye was padded but the patient failed to attend the next day.

A 39-year-old man presented with a six-month history of waking intermittently at about 3.0 am with pain in the left eye. This usually occurred after drinking six or seven whiskies. Examination showed minimal injection of the left eye and epithelial microcysts situated below the centre of each cornea but which were more marked on the left where a faint punctate stain was visible with 2 per cent fluorescein dye. Two years previously he had attended the casualty department after waking with a sore left eye. There was an area of epithelial loss in the interpalpebral zone of the left cornea and a faint epithelial irregularity extending across the right cornea. The left-sided erosion healed in 48 hours.

In many subjects, when blinking was prevented by restraining the upper lid, the tear film overlying the epithelial lesions broke down after 10 to 15 s (Fig. 3). This caused existing areas of PEK to become greyer and more readily visible and sometimes resulted in the appearance of similar greyish areas in parts of the interpalpebral cornea which had looked normal when the tear film was intact. Re-formation of the tear film resulted in rapid disappearance of these greyish areas.

Schirmer's test was performed on 22 patients, although the assessment of adequate tear production with this test is unsatisfactory because of the great variation encountered in normal individuals (de Roetth, 1953). Tear production was much reduced (less than 5 mm of wetting in 5 min) in four cases. All the patients had suffered multiple attacks and two of them demonstrated rose bengal staining of the bulbar conjunctiva on one or more visits. In the remaining 18 patients, 15 mm or more of wetting was recorded from the affected eye. In those patients on whom Schirmer's test was not performed the tear film was judged to be normal in appearance and rose bengal drops caused copious tearing in most cases.

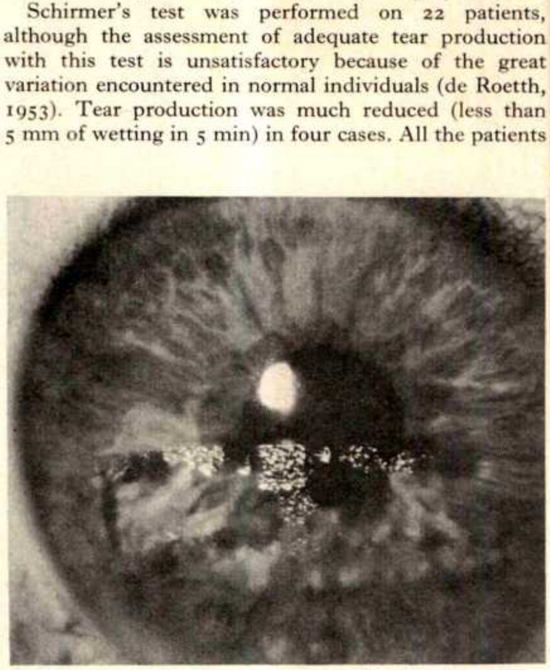

FIG. 3 *Same case as Fig. 2 (unstained). Tear film breakdown over lesion when blinking is prevented. Patient was unaware of nocturnal lagophthalmos but saw his 18-year-old son sleeping with his eyes open*

Treatment and course

Patients were treated according to the severity of their symptoms. Chloramphenicol ointment was prescribed and the eye was padded in cases in which symptoms were marked. Most patients were given chloramphenicol ointment to be used at bedtime. All patients who were seen next day were symptom-free or almost so, and the cornea had healed in most of them. In a few cases some residual epithelial lesions were still visible but these consisted predominantly of microcysts. Several patients subsequently experienced further attacks of nocturnal lagophthalmos despite the use of chloramphenicol ointment at night. However, most patients prone to recurrent attacks felt that the ointment did reduce the incidence of these attacks.

Discussion

Direct proof that the corneal lesions described in this paper were caused by exposure during sleep was obtained in only one case, although 10 other patients had been told that they sometimes slept with their eyes open. The failure to obtain such a history from the remaining patients is not surprising since most people are not observed while asleep. Even if the eyelids had been partly open during sleep a gap of 2 to 3 mm could have passed unnoticed on casual inspection, particularly in poor light.

Incomplete lid closure during sleep has however been reported by a number of authors. Fuchs and Wu (1948) described this phenomenon in China where it is not uncommon. In Bombay, Lebas (1956) encountered patients with bilateral opacification of the lower portion of the corneae which he ascribed to sleeping with the eyes half open. Likewise Mueller (1967) observed children and adults in Ethiopia who slept with their eyes open 3 to 4 mm. He surmised that this habit might in some cases produce the oval opacities on the lower third of the cornea seen in patients submitted for keratoplasty. Recently, Howitt and Goldstein (1969) in the USA described a patient, known to sleep with her eyes open, who awoke with a foreign body sensation and demonstrated punctate staining of the inferior third of both corneae. Clearly this case resembles the patients described in the present paper.

Corneal exposure will not occur if the eyes are rotated upwards during sleep, although the lids remain open. In his paper describing the motions of the eye Bell (1823) implied that during sleep the eyes are always turned upwards, this being the state of rest. In fact, Bell's phenomenon is not a constant finding during sleep. Hall (1936) examined the position of the eyes in 234 sleeping subjects and Bell's phenomenon was present in only 42 per cent. The eyes were directed straight ahead in 44 per cent and in the remainder the eyes were deviated to one side (8·5 per cent) or turned down (5·5 per cent). Hall also noted that subjects were not consistent with regard to Bell's phenomenon which might be present one night and absent the next, or vice versa.

The characteristic history given by the patients provided further evidence for the occurrence of nocturnal lagophthalmos. Thus the onset of symptoms is directly related to sleep, and once patients are awake symptoms slowly subside spontaneously. Identical symptoms may be encountered in subjects who are known to have impaired lid closure. Examples of this were seen in a patient with unilateral dysthyroid lid retraction combined with restricted elevation of the eye, and in another patient in whom unilateral congenital ptosis had been overcorrected surgically. Despite an obvious and constant cause for poor lid closure in both these patients their symptoms of nocturnal lagophthalmos occurred only intermittently, as in the patients described in this paper with normal voluntary lid closure.

Finally, the morphology and nature of the corneal lesions themselves strongly suggest that they are the result of exposure. Incomplete or partially healed lesions may take the form of a few groups of PEK scattered across the lower cornea (Fig. 4) or a collection of epithelial microcysts (Fig. 5). Viewed in isolation the aetiology of this type of epithelial disturbance is not immediately obvious. Well developed lesions, however, consist of a greyish, stippled, horizontal band lying in the interpalpebral zone, and closely resemble Ayoub's description of desiccation keratitis (Ayoub, 1944). It is curious that in half of Ayoub's cases only one eye was involved although the condition developed during the daytime. The predominantly unilateral nature of the lesions seen in nocturnal lagophthalmos is equally puzzling and remains unexplained.

The differential diagnosis of nocturnal lagophthalmos includes dendritic ulcer, incomplete blinking, and the microform of recurrent erosion.

A dendritic ulcer had been diagnosed on one or more occasions in the past in three patients who subsequently re-attended with nocturnal lagophthalmos. In two of these patients the epithelial lesions had been carbolized producing, in one case, a corneal nebula. Examination of the hospital records made at that time suggested that nocturnal lagophthalmos would have been a more appropriate diagnosis. In a fourth patient the initial diagnosis of dendritic ulcer was changed to nocturnal lago-

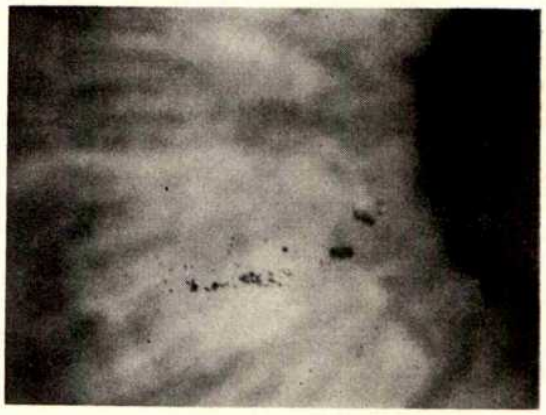

FIG. 4 *Non-specific punctate staining with rose bengal. Patient awoke twice during night with a sore eye. Seen 9 months previously with bilateral microform recurrent erosions*

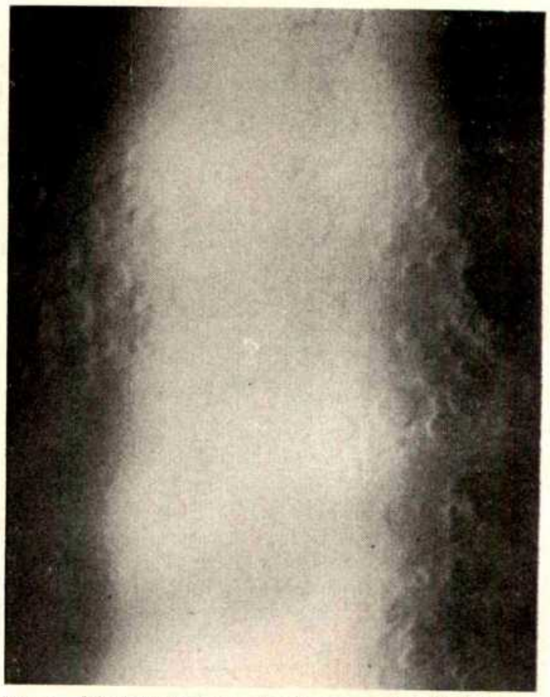

FIG. 5 *Macrophotograph showing corneal epithelial microcysts by iris retroillumination. Patient awoke with a sore eye and misty vision. No previous episodes*

phthalmos when another doctor saw the patient. The corneal lesions in all four cases were situated in the interpalpebral zone, being shown as a horizontal band of stippling in three cases, and recovery was rapid in every case. It seems unlikely that any of these four patients ever had a dendritic ulcer. It can be difficult to distinguish between a dendritic ulcer and the dendritiform figure produced during the healing stages of an epithelial disturbance. Thus in a further four patients the epithelial lesions were described as 'pseudodendritic' or 'not typically dendritic'.

Corneal staining associated with incomplete blinking has been reported in 55 out of 300 subjects who were examined before being fitted with contact lenses (Korb and Korb, 1970). 2 per cent fluorescein dye showed diffuse blotchy staining of the peripheral cornea inferiorly, unlike the pattern seen in nocturnal lagophthalmos, and no symptoms were described.

Recurrent corneal erosions occur in two forms which are distinguished by the severity and duration of the symptoms and by the epithelial changes. This was recognized by von Reuss (1898) and emphasized by Chandler (1945) who introduced the terms macro- and microform. The microform, which is more common, is characterized by the sudden onset of pain or discomfort in one eye, rarely both, which either wakes the patient from sleep or starts when the eyes are opened in the morning. Some patients notice blurred vision at the start of an attack (Franke, 1906). Symptoms subside spontaneously within minutes to hours. Depending on the facilities available and the time elapsing after the onset of symptoms, corneal examination may reveal no abnormalities (Grandclément, 1888; von Reuss, 1898; Stood, 1901; Franke, 1906), tear film disturbance when the upper lid is restrained from blinking (Peters, 1904), localized irregularities of refraction visible by skiascopy (Szili, 1900), or superficial greyish dots or flecks (Salus, 1922; Procksch, 1926) associated with microcysts (Vogt, 1930; Chandler, 1945; Bron and Tripathi, 1973) and situated below the corneal centre. Although a history of previous trauma to the affected eye is often obtained from patients with recurrent erosion, in a considerable number of cases the microform is not preceded by trauma (Szili, 1900; Franke, 1906; Salus, 1922; Procksch, 1926; Lemoine and Valois, 1930; Spektor, 1931; Chandler, 1945; Brown and Bron, 1976). Recurrences of the microform are both more frequent than the macroform and more presistent since attacks may recur for many years. The application of ointment to the eyes at night is an established prophylactic measure which greatly reduces the incidence of recurrences (von Reuss, 1898; Stood, 1901; Chandler, 1945; Thygeson, 1959).

The micro- and macroforms are thought to represent the two ends of the recurrent erosion spectrum (von Reuss, 1898; Hirsch, 1898; Szili, 1900; Salus, 1922) and both forms can occur in the same patient. Thus the microform may immediately precede the macroform in the same eye (Stood, 1901; Procksch, 1926; Brown, 1975), or both forms may appear simultaneously, one in each eye (Procksch, 1926; Brown, 1975). The frequent episodes of the microform which are encountered in some patients may be interspersed with occasional attacks of the macroform (von Reuss, 1898; Hirsch, 1898; Szili, 1900; Brown and Bron, 1976). Finally, careful examination of the epithelium surrounding a macroform erosion sometimes reveals the presence of microcysts (Bron and Tripathi, 1973; Brown and Bron, 1976), a characteristic feature of the microform.

The striking similarity between the symptoms and corneal lesions of nocturnal lagophthalmos and the microform of recurrent erosion suggests that these two conditions are identical. In this case it is likely that the macroform of recurrent erosion is also initiated by corneal exposure during sleep. This would explain why recurrences are almost invariably situated in the interpalpebral zone, but not necessarily at the exact site of the original injury in post-traumatic cases (Hirsch, 1898; Szili, 1900; Chandler, 1945; Thygeson, 1959).

Examination of the corneal lesions seen in nocturnal lagophthalmos suggested that epithelial damage might have been caused in two different ways. In most patients it appeared that evaporation of the precorneal tear film had produced desiccation of the exposed corneal epithelium. Less commonly, the lids had apparently become stuck to the cornea when the tear film and lid margin secretions dried up. Movement of the lids or globe on waking had then disrupted the superficial layers of the corneal epithelium. Thus in several patients the corneal lesions consisted of two horizontal lines of PEK parallel with the lid margin (Fig. 6). Previous authors believed that adhesion between the corneal and tarsal epithelia could cause a recurrent erosion (von Reuss, 1898), particularly when the eyes were opened abruptly (Hirsch, 1898; Sizili, 1900). Physical difficulty in opening the eyes in the morning accompanied by the onset of pain is sometimes described by patients with recurrent erosion (Stood, 1901; Hine, 1951; Bron and Tripathi, 1973; Brown and Bron, 1976). The prophylactic effect of ointment applied to the cornea at night tends to confirm the importance of exposure in the aetiology of recurrent erosion. One would expect that ointment, by augmenting the naturally-occurring oily layer of the precorneal tear film, would greatly reduce evaporation from the exposed cornea (Mishima and Maurice, 1961). This property is the

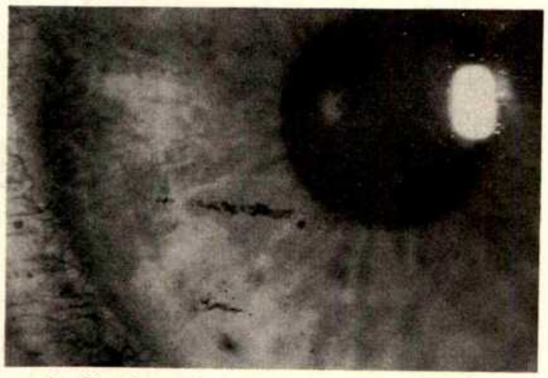

FIG. 6 *Two incomplete horizontal bands of rose bengal staining believed to represent position of upper and lower lid margins during night. Patient drank* 10 *or* 12 *pints of beer and awoke with a sore eye next day*

only factor common to the wide variety of ointments (Borlanolin, cocaine, iodoform, boric, chloramphenicol, 5 per cent NaCl) which have been recommended for the treatment and prophylaxis of recurrent erosion.

The mechanism whereby corneal exposure during sleep produces a recurrent erosion is believed to be that of damage to the superficial squamous cells of the epithelium. There is evidence that these cells represent the main barrier to the passage of tear film fluid into the epithelium (Tripathi and Bron, 1973). Exfoliation of the superficial squamous cells has been described in recurrent erosion (Tripathi and Bron, 1972) and epithelial oedema is a feature of both the traumatic (Goldman, Dohlman, and Kravitt, 1969) and the non-traumatic (Tripathi and Bron, 1972) forms of recurrent corneal erosion.

It is suggested that nocturnal lagophthalmos, by causing desiccation or disruption of the superficial epithelial cells, results in the development of epithelial oedema which, together with the epithelial damage, constitutes a microform recurrent erosion. Less commonly, fluid may accumulate beneath the epithelium to form a bulla, the rupture of which produces a macroform recurrent erosion.

The normally firm adhesion of the epithelial basement membrane to Bowman's layer may become loosened for reasons which are usually not clear, although it is known that oedema can facilitate epithelial separation (Tripathi, 1972). In post-traumatic recurrent erosion a deficiency of the basement membrane has been implicated as being a cause of the epithelial separation (Goldman and others, 1969) but in a case of non-traumatic recurrent erosion the basement membrane was found to be intact (Tripathi and Bron, 1972). It is interesting that even when the epithelium is only loosely attached, the development of a recurrent erosion is by no means inevitable. Thus Szili (1900) was able to remove almost the entire epithelium without difficulty from several asymptomatic patients who had a history of recurrent erosion whom he examined from between ten days to six weeks after their last attack. Despite the lack of epithelial adhesion demonstrated in these patients accumulation of tear film fluid beneath the epithelium was presumably prevented by the presence of an intact epithelial barrier. Damage to this barrier may be followed by bulla formation as in the patient with a history of recurrent erosions in the right eye (Salus, 1922). Soon after tonometry had been performed on this eye it became painful and a bulla was seen which subsequently ruptured. It is suggested that a commoner form of epithelial damage predisposing to macroform recurrent erosions is that caused by nocturnal lagophthalmos.

Summary

The symptoms and corneal changes caused by sleeping with one or both eyes open are described in 102 patients. The clinical picture is identical to that of the microform recurrent erosion. The close relationship between the micro- and macroforms of recurrent corneal erosion suggests that the latter condition is also precipitated by nocturnal lagophthalmos.

Many patients with nocturnal lagophthalmos were kindly referred by other doctors working in the Casualty Department and particular thanks are due to Dr Michael Quinlan.

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Nocardia asteroides keratitis
A case report

R. A. RALPH, M. A. LEMP, AND G. LISS
From the Cornea Service, Department of Ophthalmology, Georgetown University Medical Center, Washington, DC

Problems in management of ulcerative keratitis may arise from delays in diagnosis and from inadequate response to treatment. In the present case, a corneal injury was followed by *Nocardia asteroides* keratitis. The organism isolated was sensitive *in vitro* to both sulphonamides and penicillin, but there was no satisfactory clinical improvement with sulphonamides alone. Good response to treatment was delayed until topical penicillin G was added to the regimen.

Case report

An 11-year-old girl on vacation sustained an abrasion of the right eye from a fishline sinker on 26 June 1974. The eye was patched over a neomycin-polymyxin B-bacitracin ointment in the emergency ward of a local hospital. Because of persistent pain, she was examined on 2 July by her own ophthalmologist, who noted aqueous flare and cells, as well as many fine, cellular keratitic precipitates. The corneal surface centrally had a smooth, gentle concavity, without infiltrate or staining with fluorescein. To the topical antibiotics were added homatropine 5 per cent and prednisolone 1 per cent solutions, each four times daily, for treatment of the iritis. Diagnostic scraping for bacterial and fungal culture was performed on 15 July because of the reappearance of an epithelial defect. When seen in corneal consultation on 19 July the patient was using gentamicin 0·3 per cent solution every 2 hours, together with the homatropine 5 per cent and prednisolone 1 per cent solutions, each four times daily.

Uncorrected visual acuity in the right eye was 6/15, while that in the left was 6/6. The previously-noted epithelial defect had closed, but numerous greyish-white subepithelial or superficial stromal opacities were concentrated in a central, ring-like distribution of about 5 mm in diameter (Fig. 1). After repeating the diagnostic scrapings, gentamicin drops were reduced to four times daily, prednisolone 1 per cent to twice daily, and erythromycin ointment four times a day was added.

Three days later, on 22 July, cultures from the original scraping demonstrated growth of an acid-fast organism with long, branching, fragmenting hyphae. Colonies were at first chalky white, later becoming orange, and they grew on both the bottom and the surface of Sabouraud's broth. At room temperature, the organism grew slowly on Sabouraud's agar without antibiotics, on a blood agar plate (10 per cent sheep blood), and on Löwenstein-Jensen medium. It failed to grow on the Sabouraud's plate in the presence of inhibitory antibiotics. Growth on all of the above media, including those containing antibiotics, was rapid at a temperature of 35°C. There was no growth on any medium at 45°C. The organism was positive for nitrate, catalase, and urea. It failed to hydrolyze casein, xanthine, trypsin, and starch. Guinea-pig intraperitoneal inoculation allowed recovery of acid-fast organisms in 7 to 8 days. Because of the above cultural and biochemical patterns, the organism was classified as *N. asteroides*, sensitive to penicillin, ampicillin, streptomycin, and triple sulpha.

The eye was more congested by 22 July and there was generalized corneal oedema, consistent with a visual acuity of perception of light with projection. Scrapings repeated at that time demonstrated long, branching hyphae (Fig. 2), and eventually grew out *N. asteroides*. Subconjunctival ampicillin 125 mg was injected, followed by 30 per cent sodium sulphacetamide drops every hour and 10 per cent sodium sulphacetamide ointment at bedtime.

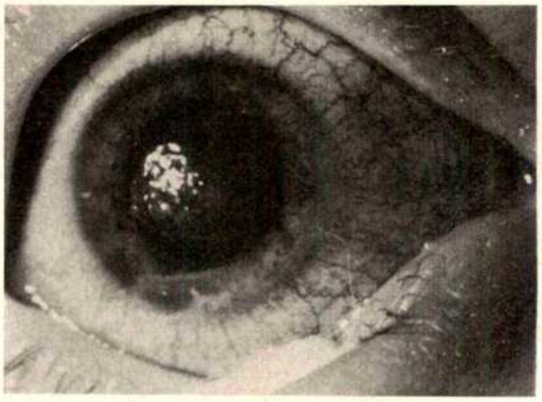

FIG. 1 Nocardia asteroides *keratitis. Three weeks after injury with a fishline sinker. Multiple superficial stromal opacities in ring-like distribution*

Address for reprints: Robert A. Ralph, MD Department of Ophthalmology, Georgetown University Medical Center, 3800 Reservoir Road, N.W., Washington, DC 20007 USA

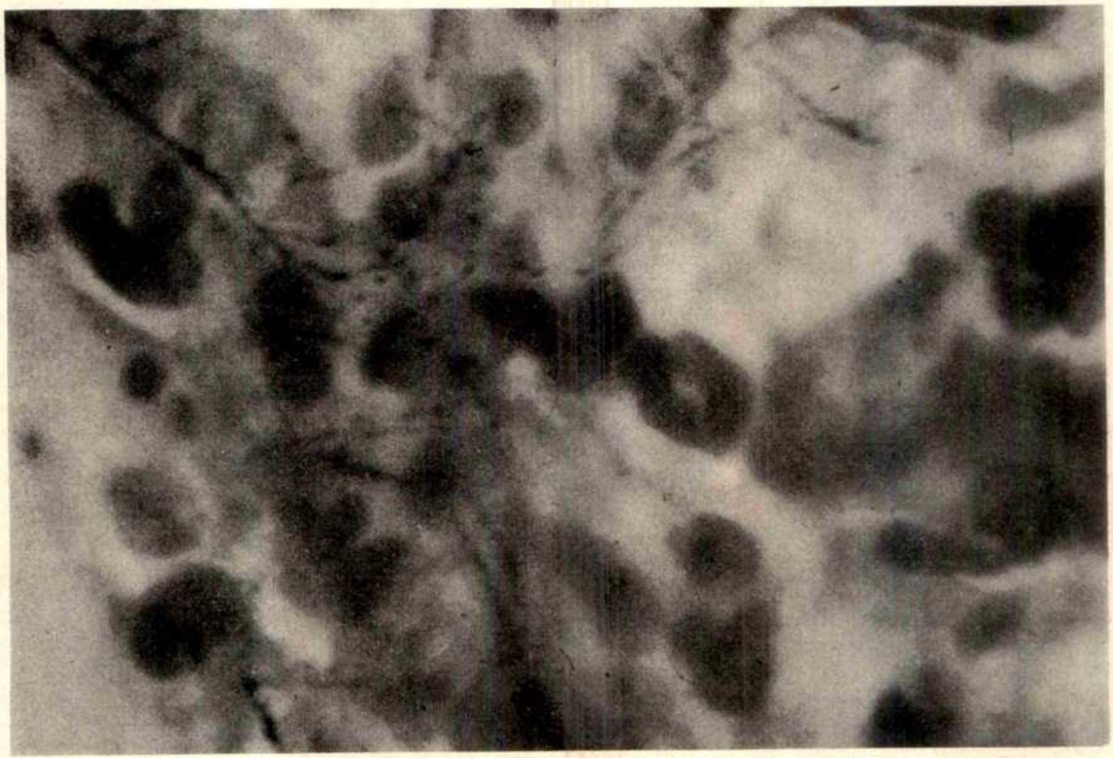

FIG. 2 Nocardia asteroides *keratitis. Scraping of lesion reveals branching hyphae among inflammatory cells. Gram stain.* × 200

The cornea improved rapidly and 5 days later there remained only a persistent ring of subepithelial punctate opacities. The lesion was once again scraped, and penicillin G drops 294 000 units per ml (in an artificial tear solution) were added, alternating hourly with the sodium sulphacetamide drops.

The remaining opacities cleared gradually, and the epithelium healed. When examined on 12 August 1974, the uncorrected visual acuity was 6/12; there was a central superficial stromal scar, with an overlying epithelium (Fig. 3). Topical penicillin was discontinued, and the sodium sulphacetamide was gradually stopped during the next 2 weeks.

Discussion

Few case reports have been published describing *N. asteroides* keratitis (Schardt, Unsworth, and Hayes, 1956; Newmark, Polack, and Ellison, 1971). In each instance, however, injury occurring outdoors has been a common factor, since a frequent source of *Nocardia* is the soil. Previous reports have not emphasized the unusual appearance of the involved eye. Lesions affect only the superficial one-third of the corneal stroma. Adjacent opacities may be arranged in a confluent, ring-like distribution, as in the present case. Eventual resolution leaves superficial stromal scarring and surface irregularities.

Nocardia asteroides is composed of gram positive, weakly acid-fast filamentous forms, with diameters of 0·5 to 1·0 μm (Fig. 2). In early cultures, branching of filaments at right-angles is distinctive, but in older colonies these tend to fragment, producing bacillary and coccoidal forms, more closely resembling bacteria than fungi (Meyer, Font, and Shaver,

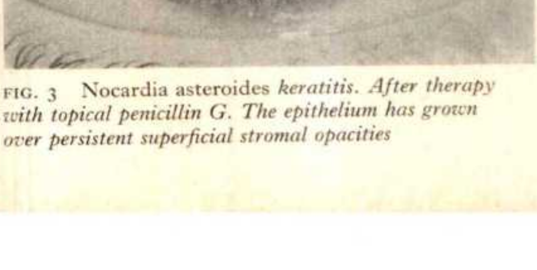

FIG. 3 Nocardia asteroides *keratitis. After therapy with topical penicillin G. The epithelium has grown over persistent superficial stromal opacities*

1970). The acid-fast characteristics are more obvious in tissue, and less evident in culture. Blood and Sabouraud's agar are good substrates for pathogenic *Nocardia*, which generally mature satisfactorily at temperatures between 35° and 37°C. Because they are slow growing, however, colonies may not be evident on the culture plates for several days. Culture media containing chloramphenicol, penicillin, and streptomycin are inhibitory to *Nocardia*, and should not be used for primary isolation if this organism is suspected (Murray, Finegold, Froman, and Will, 1961).

In most cases, *Nocardia* is sensitive to penicillin, sulphonamides, and tetracycline. The case reported by Schardt and others (1956) responded to systemic and topical oxytetracycline, while that of Newmark and others (1971) was treated successfully with systemic sulphadiazine, together with topical sulphacetamide and tetracycline.

In the present case, contamination of an injured cornea with *N. asteroides* had led to a symptomatic infection by the fifth day after the accident. As in the patient described by Newmark and others (1971), persistence of inflammation and worsening on a combination of topical antibiotics and corticosteroids prompted a vigorous search for an atypical pathogen. Indeed, the offending organism was identified, but only after the delay of one week that is often characteristic of the slow-growing *Nocardia*. Although sensitivity studies suggested that subconjunctival ampicillin and hourly sodium sulphacetamide would constitute effective treatment, only when penicillin G drops were added did the cornea clear maximally and the epithelium heal.

Summary

An 11-year-old girl developed a corneal ulcer five days after sustaining a corneal abrasion from a fishline sinker. After more than three weeks, the epithelial defect had closed, but superficial stromal opacities in a ring-like distribution had not cleared on topical gentamicin, prednisolone 1 per cent, and atropine. Several scrapings disclosed the presence of branching hyphae on smear, eventually identified as *Nocardia asteroides* by culture. Although sensitivity studies suggested that subconjunctival ampicillin and hourly sodium sulphacetamide would constitute effective treatment, resolution was only partial on this regimen. Only when penicillin G drops were added did the cornea clear maximally and the epithelium heal.

The authors wish to express their thanks to Joseph C. Stone, Mycologist, Wheaton, Maryland, USA, for his painstaking efforts in conclusively identifying the offending organism.

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A clinical evaluation of the applanation pneumatonograph

M. R. JAIN* AND V. J. MARMION
From the Bristol Eye Hospital, Bristol

The applanation pneumatonograph (PTG) is a machine which can measure the intraocular pressure, aqueous humour dynamics, and the ocular pulse. It has been developed principally by Langham and McCarthy (1968), Walker and Litovitz (1972), and Walker and Langham (1975). The instrument is a combination of a pneumatic and an electronic system. The pneumatic part of the instrument measures the intraocular pressure with the help of a small and delicate sensor that applanates the cornea and floats on an almost frictionless air bearing. The electronic part converts these measurements into electronic signals, which can be shown on the digital display or recorded on a continuous chart, providing a permanent record of the intraocular pressure, pulse, or tonography.

The merits of the instrument are threefold. It is portable and provides a continuous recording of the intraocular pressure in either the supine or sitting position. Secondly, it is possible to do tonography with easy calculation of the facility of outflow, and thirdly, a recording of the ocular pulse can be obtained. An essential element of the PTG is the sensor, see Fig. 1. This is made of plastic and covered with a thin silastic membrane which makes contact with the cornea. A gas, dichloro-difloromethane (CCl_2F_2) is passed into the system through a solenoid valve. The pressure thrusts the piston and sensor forwards causing the membrane to applanate the cornea. The pressure continues to increase until it is equal to the intraocular pressure. Since the sensor-piston is free-floating, a balance is achieved between the intraocular pressure on the one side and the gas pressure on the other, and a measurement of the intraocular pressure can thus be made. As long as the piston is allowed to float, the pressure is registered on the chart and on the digital display. A weight (Fig. 1) is applied above the disc in tonographic procedures. The whole instrument is shown in Fig. 2.

Material and methods

To compare the recordings of the PTG with those of the Goldmann tonometer, two groups of patients were examined. The first comprised 20 normal subjects (40 eyes) with an age range of 50 to 70 years, and the second a group of 35 glaucomatous patients (40 eyes) with an age range of 55 to 80 years.

The appropriate adjustments were made to the controls of the PTG. The eyes were anaesthetized with a 0·4 per cent solution of benoxinate hydrochloride. The patient was seated erect in a chair and tonometry was performed with the patient looking straight ahead. The sensor was applied to the apical zone of the cornea for about 5 seconds. Correct applanation was confirmed by a gentle whistle, and the tension was shown on the digital display and registered on the graph paper (Fig. 3). To determine the degree of reproducibility, two consecutive readings were performed at a 5 min interval. The patient was then given conventional applanation tonometry on the Haag-Streit slit lamp with a Goldmann tonometer. Both instruments were calibrated periodically, particularly the PTG, during testing.

To avoid any disturbance of the results, the ocular pulse was recorded in normal eyes 15 min after taking the intraocular pressure measurements. After necessary adjustment, the sensor was re-applied to the cornea and the ocular pulse was recorded (Fig. 4), the amplitude being calculated in mmHg.

Results

The comparative recordings of the intraocular pressure by applanation tonometry and the PTG in 40 normal eyes are shown in Fig. 5. The mean intraocular pressure was 18·25±0·25 mmHg with the PTG, and 17·5±0·19 mmHg with the Gold-

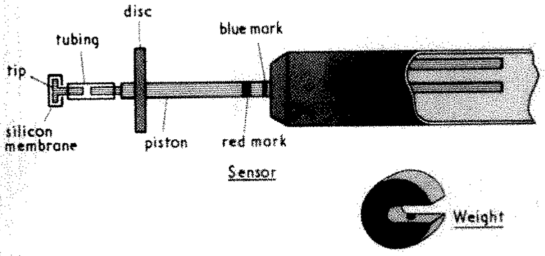

FIG. 1 *Sensor and weight*

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*Reader in Ophthalmology, Ravinder Nath Tagore, Medical College, Udaipur, India, currently a Commonwealth Fellow, Bristol Eye Hospital

Address for reprints: V. J. Marmion, FRCS, 73 Pembroke Road, Clifton, Bristol BS8 3DW

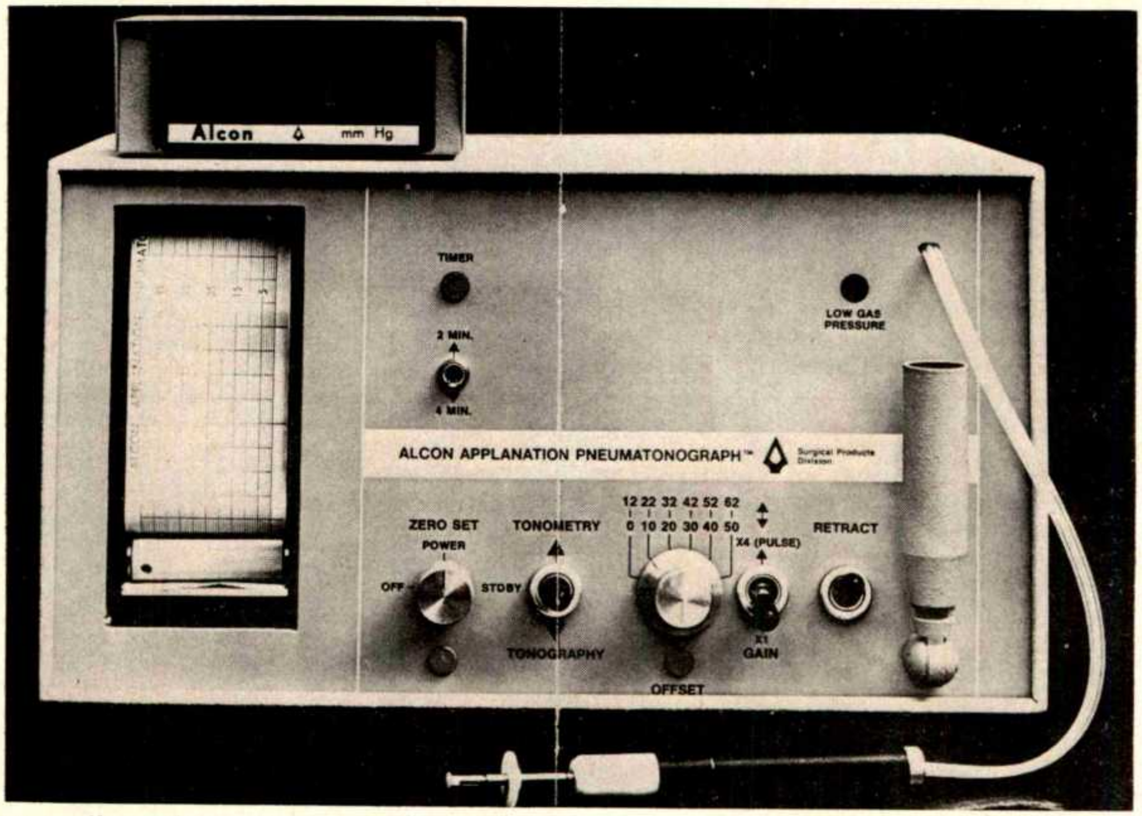

FIG. 2 *Alcon applanation pneumatonograph*

mann applanation tonometer. The PTG gave higher recordings than the Goldmann applanation tonometer. Standard deviation of readings with the PTG was 1·58 and with the Goldmann tonometer 1·17, with a correlation coefficient of 0·871.

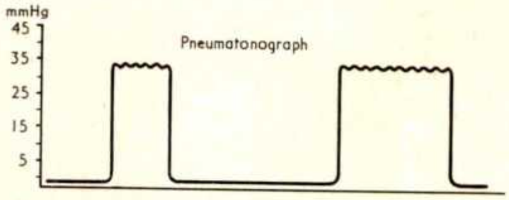

FIG. 3 *Drawing of typical pneumatonographic recording*

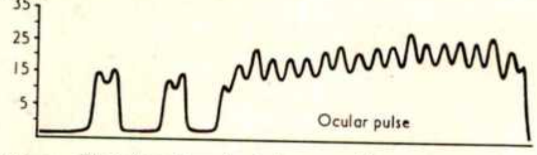

FIG. 4 *Drawing of ocular pulse recording*

Fig. 6 shows that 32·5 per cent of the normal and 30 per cent of glaucomatous eyes had the same readings with both the PTG and applanation tonometer; however, 60 per cent had higher readings with the PTG. The maximum difference was 2·5 mmHg in normal eyes and 4·5 mmHg in glaucomatous eyes.

Repeated measurements with the PTG at 5 min intervals in 40 normal eyes gave exactly similar readings in 70 per cent, higher in 20 per cent, and lower in 10 per cent.

The mean intraocular pressure in glaucomatous eyes was 35·75±1·25 and 34·5±0·75 mmHg with PTG and Goldmann tonometry, respectively; the difference was 1·25 mmHg.

In normal patients the mean ocular pulse was 3·25±0·21 mmHg (range of 2·5 to 4·5); the standard deviation was 0·35.

Discussion

Goldmann applanation tonometry has been an accurate method of measurement of intraocular pressure and the results have been shown to agree with manometrically-determined pressures. The

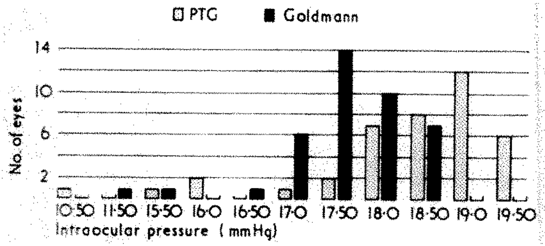

FIG. 5 *Intraocular pressure in 40 normal eyes with PTG and Goldmann tonometer*

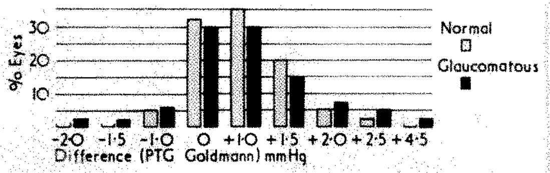

FIG. 6 *Distribution of difference between intraocular pressure in normal and glaucomatous eyes, obtained with PTG and Goldmann tonometer*

pneumatonograph gives a comparable accuracy in the recording of intraocular pressures and has the advantage of being reproducible in different postures; the influence of posture on intraocular pressure can, therefore, be more exactly determined. Applanation pneumatonography is more versatile as it is portable and does not require a slit lamp or fluorescein, and a permanent written record is available.

Our study shows that in normal and glaucomatous eyes the difference was small: 0·75 mmHg in normal and 1·25 mmHg in glaucomatous eyes. The mean difference in our series is slightly less than that reported by Quigley and Langham (1975) in 100 normal eyes. The correlation coefficient of 0·871 is highly significant suggesting a good agreement between the PTG and the Goldmann readings. It must, however, be noted that the difference between the PTG and the Goldmann readings tends to increase with the higher pressures and particularly in glaucomatous cases.

Moses and Liu (1968) showed that there was a mean pressure difference of 2 mmHg in 35 per cent of eyes after repeated Goldmann tonometry.

As stated, repeated measurements showed no difference in 70 per cent of cases and only a slight difference in the remainder, suggesting that the external force applied in this technique is comparatively less than with the Goldmann tonometer. This finding makes the PTG more acceptable for dose-response studies where frequent readings at short intervals are essential.

The mean intraocular pressure in the normal patients examined compares poorly with normal pressures as reported by Tierney and Rubin (1966), Becker and Shaffer (1961), and Armaly and Salamoun (1963), but reasonably well with recent studies of Quigley and Langham (1975) (Table). The variation with earlier authors is probably due to the different age group examined. Our normal cases were between 50 and 70 years of age and, therefore, are more comparable with the glaucomatous group, and representative of a normal ageing population.

The amplitude of ocular pulse as analysed in 40 normal eyes had a mean value of 3·25±0·21 mmHg (range of 2·5 to 4·5). This is close to that reported by Bynke (1968), Best and Rogers (1974), and Quigley and Langham (1975).

It was, however, observed that, in cases with an ocular pulse of more than 3 mmHg, visual estimation of the point of inner ring contact in Goldmann tonometry introduces an important variation in readings, whereas the PTG provides a graphic recording of systolic and diastolic pulse pressure. Moreover, its readings do not have the potential inaccuracy of visual mean estimation nor the possible bias of a hand-operated scale as with the Goldmann tonometer.

An important advantage of the PTG over the Goldmann lies in its ability to measure intraocular pressure independent of posture. This provides a simpler means of studying the postural effects of intraocular pressure on individual eyes. The mean pressure increment in normal eyes, as noted by

Table *Comparison of means and standard deviations of applanation readings*

Method	*PTG*		*Goldmann tonometry*				
Authors	*Jain and Marmion*	*Quigley and Langham*	*Tierney and Rubin*	*Becker and Shaffer*	*Armaly and Salamoun*	*Quigley and Langham*	*Jain and Marmion*
Date	1975	1975	1966	1961	1963	1975	1975
Mean	18·25±0·25	21·50±0·81	16·23	15·40	14·73	20·2±1·0	17·50±0·19
Standard deviation	1·59	2·83	2·50	—	—	—	1·19

Langham (1974), Armaly and Salamoun (1963), and Langham and McCarthy (1968), was 2·1, 2·63, and 1·78 mmHg, respectively. The postural difference in pressure is of significance in the diagnosis of borderline cases of glaucoma, particularly those where the postural element is marked.

The correct application of the sensor to the cornea is confirmed by a whistle emitted from the PTG. The sensor tip is generally applied to the apical zone of the cornea for convenience and quick results, but it can also be applied to paracentral or para-apical zones with satisfactory results. This fact was confirmed in a few of our cases and we were successful in determining the intraocular pressure in two cases of central corneal ectasia where neither Goldmann nor Schiötz tonometry was possible. Its comparatively gentle touch and ability to record pressure in any position, without the use of fluorescein, enable the recording of pressures in the immediate postoperative period and in patients wearing soft contact lenses.

Summary

The applanation pneumatonograph combines pneumatic and electronic systems. It is used for measuring intraocular pressure, aqueous humour dynamics, and ocular pulsation.

In the present study the PTG and the Goldmann tonometer have been used to measure the intraocular pressure in 40 normal and 40 glaucomatous eyes. It has been found that the results of the two instruments correlate well. The PTG readings have, generally, been found to be higher with a mean difference of 0·75 mmHg in the normal and 1·25 mmHg in the glaucomatous eye.

The mean ocular pulse as determined in normal eyes was 3·25±0·21 mmHg.

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Postural change and intraocular pressure in glaucomatous eyes

U. W. WÜTHRICH
Switzerland

Several authors (Anderson and Grant, 1973; Galin, McIvor, and Magruder, 1963; Hetland-Eriksen, 1966; Kriegelstein and Langham, 1975a; Roberts and Rogers, 1964; Tarkkanen and Leikola, 1967) have reported that in normal subjects and in glaucomatous patients the intraocular pressure (IOP) in the supine position is about 2–5 mmHg higher than in the seated position. The measurements were carried out using various types of tonometers.

The object of the present study was to investigate the postural response of intraocular pressure, using the pneumatonograph mod. 40* (PTG), the Perkins hand-held tonometer, and the Goldmann tonometer. The PTG gives an instantaneous and continuous record of the intraocular pressure. It was described by Langham and McCarthy (1968), and the results of clinical trials were reported by Geib, Kriegelstein, and Waller (1974); it would seem to be particularly suitable for recording the IOP in various postures. In this study the Goldmann applanation tonometer attached to a Haag-Streit slit lamp mod. 900 was used for the sitting position, and the Perkins hand-held tonometer (Perkins, 1965) and the PTG were used for the seated and supine positions. Good agreement between readings of the Perkins tonometer and the Goldmann tonometer has been reported (Dunn and Brubaker, 1973; Kriegelstein and Waller, 1975; Flament, 1969; Whitty, 1969; Wallace and Lovell, 1968).

Material and methods

The PTG was used as suggested by Langham and McCarthy (1968), but only in the × 1 gain code. Pressure calibrations were performed in the vertical and horizontal positions, using a human cornea clamped in a Perspex chamber which was filled with water and connected to a manometer; the stopcock was left open. The sensor was clamped in a stand and the tip of the sensor was brought mechanically into contact with the cornea, so that a reproducible reading could be obtained.

The clinical tests were carried out in the Glaucoma Clinic at the Institute of Ophthalmology in London on 53 outpatients of both sexes who had primary glaucomas of various types. Some eyes were receiving medical treatment and some had had drainage surgery. The three tonometers were used in sequence on patients in the seated position, first on the right eye, then on the left. Tight clothes were loosened before the measurements were taken and each patient was asked to lie flat without a pillow for measurements in the supine position using the Perkins tonometer and the PTG. The eyes were anaesthetized with a mixture of oxybuprocaine and fluorescein (Fenton, 1965). All measurements were carried out by the same investigator and repeated three times on each eye and with each instrument 3–5 min after changing position.

Results

CALIBRATION

With the Perspex chamber arranged for horizontal application of the tonometer the calibration was linear from 5 to 30 mmHg and the readings were identical with those of the manometer (Fig. 1). It was found possible to obtain higher readings by increasing the pressure on the sensor against the

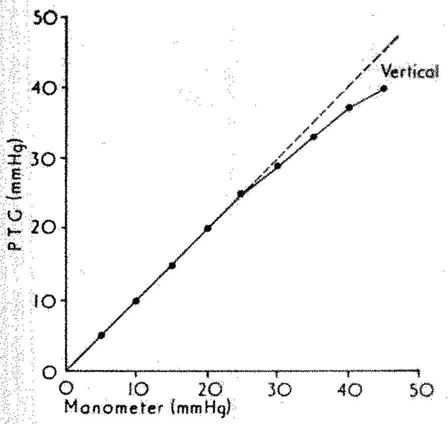

FIG. 1 *Calibration of PTG for horizontal application of sensor. (Corresponding to vertical position of patient)*

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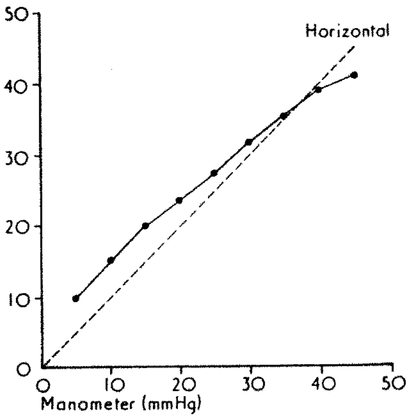

FIG. 2 *Calibration of PTG for vertical application of sensor. (Corresponding to horizontal position of patient)*

cornea without any alteration to the quality of the sound signal, which is said to act as a control for false readings. The recordings with vertical application of the tonometer showed higher readings (up to 30 mmHg), while above 35 mmHg the readings were lower than those of the manometer (Fig. 2).

CLINICAL TESTS

The mean values of the intraocular pressure measurements in 105 eyes are shown in Table I. No significant difference could be found between the Goldmann and the Perkins tonometric measurements in the seated position, Table II. Highly significant differences resulted, however, when the Perkins tonometric and the PTG readings in the seated and supine position were compared.

Fig. 3 shows the Perkins and Goldmann tonometric readings and Figs 4 and 5 show the Perkins tonometric and the PTG readings, plotted for different positions. Table III shows the frequency of discrepancies between the PTG and the Perkins tonometer readings in the present study. The discrepancy can be reduced if the PTG readings are corrected by −4 mmHg for the seated position and −3 mmHg for the supine.

Discussion

The significant increases in IOP on changing from the sitting to the supine position of 4·1 mmHg

Table I *Mean readings and standard deviations of IOP in 105 glaucomatous eyes measured with Goldmann tonometer in seated position, and with Perkins tonometer and PTG in seated and supine position*

Tonometer	*Mean value ± SD (mmHg)*	
	Seated	*Supine*
Goldmann	20·42±5·01	—
Perkins	20·20±5·01	24·34±5·67
PTG	24·34±4·96	27·06±4·79

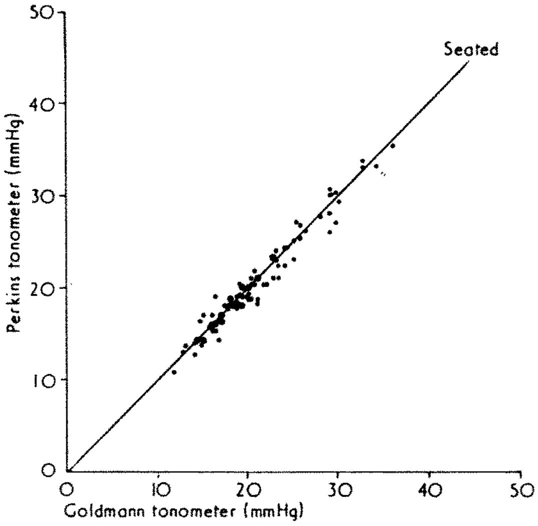

FIG. 3 *Comparative IOP measurements with Goldmann and Perkins tonometers in series of 105 glaucomatous eyes in seated position*

Table II *Mean differences, significance, and correlation coefficients of IOP in 105 glaucomatous eyes using Goldmann tonometer in seated position, and Perkins tonometer and PTG in seated and supine position*

Tonometer	*Mean difference ± SD (mmHg)*		*Significance of the mean difference*	*Correlation coefficient*
	Seated	*Supine*		
Goldmann/Perkins	−0·22±0·94		Not significant	0·978
Goldmann/PTG	+3·93±2·30		P<0·0005	0·887
Perkins/PTG	+4·14±2·11		P<0·0005	0·901
Perkins/PTG		+2·74±2·77	P<0·0005	0·864

Table III *Differences in PTG and Perkins tonometric readings as found in this study compared with PTG readings corrected by -4 mmHg in seated and -3 mmHg in supine position*

Difference PTG-Perkins T (± mmHg)	*No. of readings*		*PTG readings corrected by*	
	Seated	*Supine*	*-4 mmHg Seated*	*-3 mmHg Supine*
Up to 1	14	33	52	48
2 or 3	25	40	43	34
4 or above	66	32	10	23

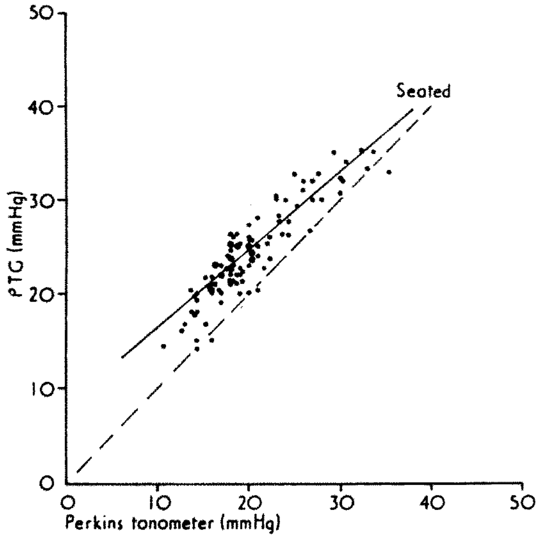

FIG. 4 *Comparative IOP measurements with Perkins tonometer and PTG in series of 105 glaucomatous eyes in seated position*

with the Perkins tonometer and 2·8 mmHg with the PTG are comparable with the measurements of Geib and others (1974) and other workers.

The accuracy of the PTG is worth some discussion. The PTG showed a mean reading of 3·9 mmHg higher than that of the Goldmann tonometer and 4·1 mmHg higher than the Perkins tonometer in the seated position; it was 2·6 mmHg higher than the Perkins tonometer in the supine position. Geib and others (1974) found in their study that an average reading of the PTG was 2·9 mmHg higher than that of the Goldmann tonometer. Kriegelstein and Langham (1975b) subtracted 2 mm Hg from readings, when using the PTG in their work on low-tension glaucoma.

In the present study 63 per cent of PTG readings differed by 4 mmHg or more when compared with the readings of the Perkins tonometer in the sitting position, the corresponding figure in the supine position being 30 per cent. Subtracting 4 mmHg from the PTG readings in the sitting position and 3 mmHg in the supine position reduces the discrepancy between the two methods. Such a correction does not alter the rather large scatter of PTG readings compared with the Goldmann or Perkins tonometer readings. In clinical practice accurate tonometry is important at the upper level of normal pressures, approximately 21 mmHg; at this level the PTG readings differed from the Goldmann reading by -3 to +10 mmHg in the sitting position and by -4 to +12 mmHg from the Perkins tonometer readings in the supine position.

It should be pointed out that the PTG used in this study was an early model, but the satisfactory calibration curves obtained on the isolated human cornea suggest that the instrument was working correctly. The discrepancies between PTG readings and those of other tonometers could have

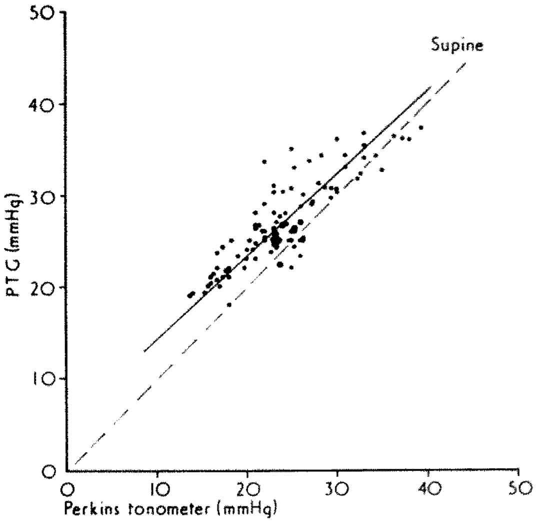

FIG. 5 *Comparative IOP measurements with Perkins tonometer and PTG in series of 105 glaucomatous eyes in supine position*

resulted from variations in the position of the sensor on the cornea and the higher mean readings probably resulted from an indentation of the cornea causing an increase in IOP. A modified sensor with a pneumatic bearing to limit this effect has been described (Walker and Langham, 1975).

Conclusions

In glaucomatous eyes the IOP was found to be 3–4 mmHg higher in the supine position than in the seated position when the pressure was measured 3–5 min after the change in position. The accuracy of an early model of PTG mod. 40 did not seem to be entirely satisfactory.

I should like to express my gratitude to Professor E. S. Perkins and Dr J. Gloster for permitting me to perform this study and for their advice, to Mr B. Augier for the calculations, and to the staff of the Special Clinics and the Department of Experimental Ophthalmology for their kind help.

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Provocative tests in closed-angle glaucoma

R. MAPSTONE
From St Paul's Eye Hospital, Liverpool

The absence of a provocative test with proved predictive value, in eyes at risk of developing closed-angle glaucoma, creates many problems—for example, a patient presents with a family history of acute closed-angle glaucoma and has narrow angles. What is the probability of his developing an acute attack?

Gonioscopy is of no help in answering this question since an assessment of the narrowness of an angle is a subjective one. If—on the basis of gonioscopy findings—an angle is thought to be capable of closure then three options are open to the ophthalmologist:

1. All such eyes require prophylactic iridectomy
2. Some such eyes require iridectomy
3. Gonioscopy provides insufficient evidence on which to base a decision and therefore other criteria must be invoked.

The first option is rarely, if ever, adopted. The second option is logically inconsistent, and the third a reasonable inference. It is perhaps relevant to mention that it is unnecessary to perform gonioscopy to determine the narrowness of an angle. Van Herrick and Shaffer (1969) showed that moving the slit beam to the corneal side of the limbus is—with practice—just as informative on this point.

Again, no prospective studies are available to show which narrow angle will close—indeed, there would be no point in such a study because one would merely be left with one group of (gonioscopically) narrow angles that occluded and another group that did not, but with insufficient quantitative data on which to base a decision in a particular eye.

A more useful approach would be to devise a provocative test scheme from which it could be inferred with a high degree of probability that a *particular* eye would (or would not) develop angle closure. Such a scheme would have the following characteristics:

1. A sound theoretical and experimental basis
2. Simplicity
3. Speed (not time-consuming)
4. Reproducibility
5. No false positives
6. No false negatives
7. No danger to the patient
8. It would be within the limits of normal experience, that is, physiological.

It is probable that these criteria will prove difficult to meet. The purpose of this paper is to describe and illustrate a scheme which goes some way towards that goal.

Material and methods

Altogether 119 eyes from 100 patients were selected for provocative testing on the basis of the following criteria:

1. Acute closed-angle glaucoma in the contralateral eye
2. Chronic closed-angle glaucoma in the contralateral eye
3. A history of intermittent closed-angle glaucoma in one or both eyes
4. A central retinal vein occlusion in the contralateral eye associated with narrow angles.

Each eye was provoked as follows:

At zero hours a photograph of the anterior segment was taken. Pilocarpine drops 2 per cent and phenylephrine drops 10 per cent were instilled alternately three times at 1 min intervals, and the intraocular pressure was recorded. Subsequently, at approximately half-hourly intervals, phenylephrine 10 per cent was instilled, an anterior segment photograph was taken, and the intraocular pressure recorded. As soon as the intraocular pressure had increased significantly (more than 8 mmHg) intravenous acetazolamide 500 mg, thymoxamine drops 0·5 per cent, and pilocarpine drops 2 per cent were instilled. Pressures were measured and anterior segment photographs were taken thereafter at approximately hourly intervals. The slides were subsequently projected and P/C* ratios calculated in the horizontal meridian.

If, after 2 h, the above test was negative then a further dose of pilocarpine 2 per cent was instilled, together with 10 per cent phenylephrine, and the test continued as described above. If, 1½ h later, the intraocular pressure had not increased, thymoxamine drops 0·5 per cent were instilled to terminate the test.

On another day, eyes that were negative to the pilocarpine and phenylephrine test were re-provoked as follows:

At zero hours an anterior segment photograph was

Address for reprints: R. Mapstone, St Paul's Eye Hospital, Liverpool L3 9PF

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*P/C = Pupillary and corneal diameters

taken, tropicamide drops 0·5 per cent three times at 1 min intervals were instilled, and the intraocular pressure was recorded. Subsequently, at approximately half-hourly intervals, an anterior segment photograph was taken and the intraocular pressure recorded. As soon as the intraocular pressure had increased significantly, with evidence of angle closure, intravenous acetazolamide 500 mg was given and pilocarpine 2 per cent instilled. If after 2 h the pressure increase was less than 8 mmHg, pilocarpine 2 per cent was instilled and the test terminated.

Gonioscopy was not routinely done; the presence of partial or complete angle closure can be quickly and adequately determined by moving the slit beam to the corneal side of the limbus in the four quadrants.

Results

Fig. 1 shows that 66 (55·5 per cent) were positive with simultaneous pilocarpine and phenylephrine alone. This figure is increased by eight to 74 (62 per cent) if additional pilocarpine was instilled after 2 h, in the patients who were initially negative with simultaneous pilocarpine and phenylephrine. Of the remaining 45 patients nine (8 per cent of the total) were subsequently positive on re-provocation with tropicamide. Thus, of the 119 eyes, 83 (70 per cent) responded to provocative testing with a positive result; 36 or 30 per cent were negative.

The eyes provoked, therefore, fell into four groups:

1. Simultaneous pilocarpine and phenylephrine produced a positive result (66 or 55 per cent)
2. Additional pilocarpine was necessary to provoke angle closure (8 or 6·7 per cent)
3. Pilocarpine and phenylephrine were negative but tropicamide was positive (9 or 7·6 per cent)
4. Neither test was positive (36 or 30 per cent).

The mean statistics relating to these four groups are shown in the Table under the following headings:

1. Number of eyes
2. Time interval (min) between start of provocative test and rise in intraocular pressure
3. Time between second dose of pilocarpine and rise in pressure
4. Rate of rise in intraocular pressure
5. Increase in intraocular pressure
6. Total time taken
7. P/C ratio at onset of rise in pressure
8. P/C ratio at second instillation of pilocarpine
9. P/C ratio at termination of provocative test
10. Maximum P/C ratio with pilocarpine and phenylephrine
11. Maximum P/C ratio with tropicamide.

The results for the simultaneous pilocarpine and phenylephrine group are summarized in Fig. 2. After 63 min the intraocular pressure began to increase at a P/C ratio of 0·37. The increase in pressure was 21·5 mmHg; 79 min after intravenous acetazolamide, the intraocular pressure had resumed a normal level and the P/C ratio fallen to 0·23. The total time taken was 2 h 22 min.

The results for the eight patients in the simultaneous pilocarpine and phenylephrine group in whom additional pilocarpine was necessary to provoke angle closure are summarized in Fig. 3. All times were at least doubled—after 3 h 5 min the intraocular pressure began to rise (on average 34 mmHg) at a P/C ratio of 0·40 (having decreased from 0·43). After intravenous acetazolamide the

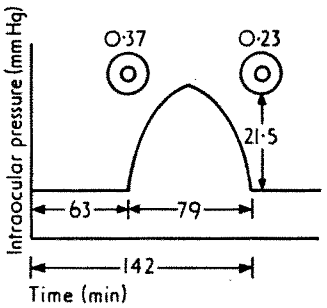

FIG. 2 *Mean statistics of eyes provoked to angle closure by simultaneous instillation of pilocarpine and phenylephrine. P/C ratios at angle closure and termination of test are shown*

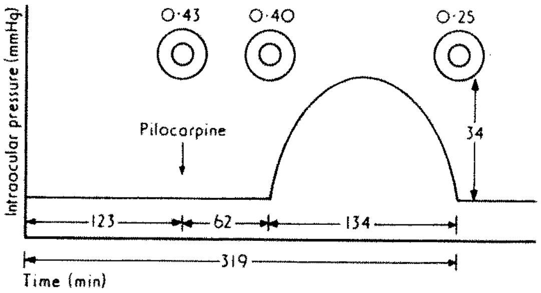

FIG. 3 *Mean statistics of eyes provoked to angle closure by simultaneous instillation of pilocarpine and phenylephrine, in which additional pilocarpine was necessary. P/C ratios at instillation of pilocarpine, angle closure, and termination of test are shown*

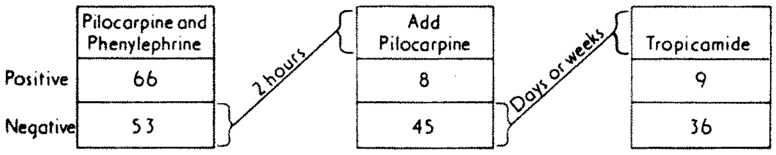

FIG. 1 *Results of provocative tests with pilocarpine, phenylephrine, and tropicamide*

pressure resumed a normal level 2 h 14 min later and the P/C ratio had fallen to 0·25. The total time taken was 5 h 19 min.

The results for the nine patients in whom provocation with pilocarpine and phenylephrine was negative, but re-provocation with tropicamide was positive, are summarized in Fig. 4. After 47 min intraocular pressure began to increase (on average 22·7 mmHg) at a P/C ratio of 0·52. After intravenous acetazolamide, 77 min later, the pressure had fallen to normal at a P/C ratio of 0·3. The total time taken was 2 h 4 min.

Application of Student's *t* test to any P/C ratio (Table) from pilocarpine and phenylephrine provocative tests (positive or negative), in any combination taken two at a time, shows no significant difference. Similarly there is no significant difference between positive and negative tropicamide P/C ratios. There is however a significant difference between any pilocarpine and phenylephrine ratio and any tropicamide ratio (at the 1 per cent level).

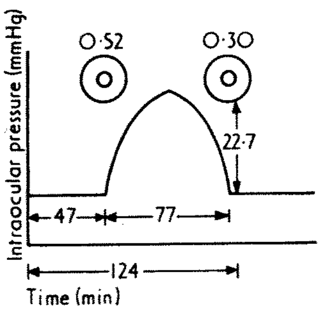

FIG. 4 *Mean statistics of eyes provoked to angle closure by tropicamide. P/C ratios at angle closure and termination of test are shown*

The mean age of the patients in the simultaneous pilocarpine and phenylephrine positive group was 62·8 years (range 34 to 80). For the group in whom all provocative tests were negative the mean age was 65·6 years (range 48 to 84). Application of Student's *t* test to these two means showed no significant difference.

Discussion

The theoretical and experimental basis for this approach to provocative testing has been discussed in previous papers (Mapstone, 1974a, b, c, 1976) and depends on the following considerations:

a. The pupil blocking force—and therefore pupil block—is due mainly to the sphincter muscle.
b. Angle closure most commonly occurs at around mid-dilatation.
c. Hence to provoke angle closure the ideal situation would be a mid-dilated pupil in the presence of increased sphincter activity. This is achieved by instilling phenylephrine and pilocarpine simultaneously. The former produces just sufficient dilatation to allow enhanced sphincter activity—produced by pilocarpine—to increase pupil block. The pressure of aqueous in the posterior chamber then 'pushes' a lax iris on to the cornea and closes the angle.
d. It has also been shown that additional pilocarpine—after the simultaneous instillation of pilocarpine and phenylephrine—can precipitate angle closure by a mechanism independent of a significant change in sphincter

Table *Mean statistics obtained during provocative testing*

Test	*Pilocarpine and phenylephrine positive*	*Pilocarpine and phenylephrine pilocarpine positive*	*Pilocarpine and phenylephrine negative tropicamide positive*	*Pilocarpine and phenylephrine negative tropicamide negative*
Number of eyes	66	8	9	36
Time between start of test and rise in pressure (min)	63	185	47	—
Time between second pilocarpine instillation and rise in pressure	—	62	—	—
Rate of rise in pressure (mmHg/min)	1 in 3·7	1 in 1·8	1 in 4·5	—
Increase in pressure (mmHg)	21·5	34	22·7	—
Total time taken (min)	142	319	175	—
P/C ratio at angle closure	0·37	0·40	0·52	—
P/C ratio at second pilocarpine instillation	—	0·43	—	—
P/C ratio at end	0·23	0·25	0·3	—
Maximum P/C ratio with pilocarpine and phenylephrine	0·37	0·43	0·37	0·38
Maximum P/C ratio with tropicamide	—	—	0·52	0·51

activity. It was suggested that the additional mechanism was an increase in trabecular meshwork outflow 'pulling' the iris on to the cornea.

e. Finally, it was shown that in some eyes too much parasympathetic activity precludes the development of angle closure, but that, with a mid-dilated pupil obtained by parasympathetic inhibition (tropicamide), pupil block was sufficient to allow the pressure in the posterior chamber to 'push' the iris on to the cornea.

The remaining criteria for an ideal provocative scheme mentioned in the introduction are not completely fulfilled:

By no yardstick can the tests be considered difficult and 90 per cent are complete within 2½ h. There remain, however, 10 per cent (the simultaneous pilocarpine, phenylephrine, and additional pilocarpine group) in whom the test takes approximately 5 h—although basic ophthalmic care is necessary only after 3 h. No doubt these times could be shortened by measuring pressures more frequently. There has to date been one false negative (see below) and false positives are by their very nature impossible to prove—since a positive provocative test cannot be ignored. The question whether these tests are 'physiological'—that is, within the limits of the possible autonomic stress to which an eye may be exposed—must also be considered.

Parasympathetic inhibition and excitation present no problem since they have their clinical counterpart in the dark room and reading provocative tests. Combined maximal sympathetic and parasympathetic stimulation does however present difficulties. It is possible to conceive of situations in which this can happen—for example, reading a salacious novel—but does not constitute proof. Finally, there was no evidence to show that any eye lost vision or field as a result of a positive provocative test.

The significance of parasympathetic activity in precipitating angle closure is well illustrated by the results of provocative testing with simultaneous pilocarpine and phenylephrine. In the 66 eyes that developed closed-angle glaucoma, sphincter muscle activity was at a near maximum and the pupil mid-dilated, ideal conditions for developing 'push' closed-angle glaucoma. However, a further eight patients developed closed-angle glaucoma only after the instillation of a second dose of pilocarpine (Fig. 3). The change in pupil diameter (and hence pupil blocking force) was not statistically significant, so that an additional parasympathetic mechanism was necessary. It has already been suggested that an increase in trabecular meshwork outflow is the most probable result—in effect 'pulling' the iris on to the cornea.

That nine eyes developed a positive test with tropicamide but were negative with simultaneous pilocarpine and phenylephrine presents something of a paradox. There is a significant difference between the P/C ratios of eyes at angle closure induced by pilocarpine/phenylephrine and tropicamide. Furthermore, eyes that were positive with tropicamide had already responded negatively to pilocarpine/phenylephrine and, between the P/C ratios for (negative) pilocarpine/phenylephrine and (positive) tropicamide tests in the same eye, there was a significant difference. It is a necessary consequence, therefore, that in some anterior segments too much parasympathetic activity precludes the development of angle closure, the most probable explanation being that with a smaller pupil diameter the iris is too taut to become sufficiently *bombé* to close the angle. With tropicamide the pupil diameter is larger and the iris more lax, but pupil block significantly reduced. Nevertheless angle closure still occurs, and it must be concluded that in some eyes a minimal pupil blocking force is sufficient to produce angle closure—that is, this form of closed-angle glaucoma is precipitated by pupil block alone.

The 36 eyes in which all tests were negative form an interesting group. In five there was significant anisometropia with amblyopia although it was not always the more hypermetropic eye that developed an acute attack. As a group, however, there was no significant difference between the P/C ratios attained during provocative testing as compared with the positive groups; it is reasonable to conclude that autonomic drug delivery in all groups (positive and negative) was therefore the same. It could be argued that the anatomical peculiarities of these anterior segments were such that, no matter what the manipulation of the autonomic nervous system might be, angle closure would not develop. In particular, the shallowing of the anterior chamber with age that depends on lens growth is as yet insufficient. With the passage of time such a decrease will occur and then allow angle closure to develop. There is, however, no significant difference between the ages of positive and negative groups which, if present, would have supported the anatomical argument.

Finally, it could be asserted that there is no reason to suppose that these eyes will develop closed-angle glaucoma. Consequently, it was decided not to do prophylactic peripheral iridectomies nor to treat with miotics. The 36 eyes have been followed-up for a period of 1 to 7 years (mean follow-up 3 years), and to date, only one has developed acute closed-angle glaucoma 3 months after provocative tests were done. Throughout the period of follow-up each eye has been re-provoked, at roughly yearly intervals, with tropicamide and

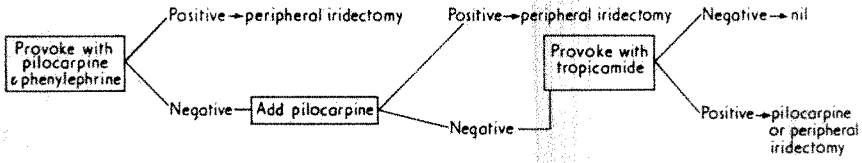
Provoke with pilocarpine c phenylephrine
Positive → peripheral iridectomy
Negative
Add pilocarpine
Positive → peripheral iridectomy
Negative
Provoke with tropicamide
Negative → nil
Positive → pilocarpine or peripheral iridectomy

FIG. 5 *Provocative test scheme*

simultaneous pilocarpine/phenylephrine alternately. Data obtained from the series by Lowe (1962) indicate that at least 12 eyes should have developed acute attacks if they, as a group, did not differ from other contralateral eyes at risk. The evidence is by no means conclusive, but it seems reasonable to extend both the period of follow-up and the number of eyes.

Published series indicate that not all eyes at risk subsequently develop closed-angle glaucoma—for example, Adams (1955) 46 per cent, Kronfeld (1956) 50 per cent, Winter (1955) 32 per cent, Bain (1957) 47 per cent, and Lowe (1962) 49 per cent. It would seem, however, that a follow-up period of 10 years is necessary before the true predictive value of a provocative test scheme can be determined. The negative results in the 36 patients described here indicate only that there is no pressing urgency for iridectomy, not that iridectomy is unnecessary. Indeed, it would be unwise to ignore evidence that routine iridectomy in contralateral eyes is—in general—the more prudent of the alternatives (Blaxter and Chatterjee, 1960; Douglas and Strachan, 1967). The intention is not to question that evidence, but to delineate a group of patients who have a high probability of developing closed-angle glaucoma yet do not develop positive provocative tests. The prospective study of these patients may eventually provide information of great relevance to the management of eyes with (gonioscopically) narrow angles.

Again, the patients who are tropicamide positive but phenylephrine/pilocarpine negative form an interesting group, in whom it is reasonable to suppose that too much parasympathetic activity precludes the development of closed-angle glaucoma. Logically, therefore, the use of pilocarpine would be an effective prophylactic and an iridectomy would be unnecessary.

A suggested scheme for provocative testing is therefore as follows (Fig. 5):

1. All eyes at risk are provoked with simultaneous pilocarpine and phenylephrine. If the test is positive, a peripheral iridectomy is done.
2. If after 2 h the test is negative then additional pilocarpine is instilled. If the result is positive, a peripheral iridectomy is done.
3. If the result is negative, re-provoke with tropicamide. If this is negative no treatment is indicated but follow-up is required. If the result is positive an iridectomy should be done or pilocarpine prescribed.

Summary

Altogether 119 eyes at risk of developing closed-angle glaucoma were provoked with simultaneous pilocarpine and phenylephrine; of these 74 developed closed-angle glaucoma. The remaining 45 eyes were re-provoked with tropicamide and a further nine developed closed-angle glaucoma.

The 36 eyes in which all tests were negative were given no treatment and have been observed for a period of 1 to 7 years (mean 3 years). One has developed closed-angle glaucoma.

A scheme for provoking eyes at risk of developing closed-angle glaucoma is described.

I should like to thank colleagues who referred patients, Mr R. McBride for preparing the diagrams, and Miss E. Grogan for secretarial help.

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The syndrome of closed-angle glaucoma

R. MAPSTONE
From the St Paul's Eye Hospital, Liverpool

Since Barkan (1938) first clearly distinguished between open- and closed-angle glaucoma (CAG), attention has been directed intermittently to precipitating angle closure (AC), by creating an experimental situation in which it can be predicted with a high degree of probability that a particular eye will develop CAG.

The methods used have mainly depended upon manipulating the autonomic nervous system:

1. Parasympathetic inhibition (dark room tests, parasympatholytic drugs)
2. Sympathetic stimulation (phenylephrine)
3. Parasympathetic stimulation (reading provocative tests, miotics)
4. Combined sympathetic and parasympathetic stimulation (pilocarpine and phenylephrine).

Such a varied group of precipitating events does not bespeak a unitary disease. The purpose of this paper is to define the main clinical syndromes, and explain apparent inconsistencies.

Material and methods

A method for provoking eyes which are at risk of developing CAG by using pilocarpine and phenylephrine simultaneously has been described previously (Mapstone, 1974c). Altogether 20 eyes of 20 patients who each reacted positively to pilocarpine and phenylephrine, were re-provoked with 0·5 per cent tropicamide. Drops were instilled three times initially at 1 min intervals, an anterior segment photograph taken, and the intraocular pressure (IOP) was measured. Thereafter, at approximately half-hourly intervals, the IOP was measured and a photograph of the anterior segment was taken. As soon as the IOP had risen significantly (more than 8 mmHg) with gonioscopic evidence of partial or complete AC, intravenous acetazolamide (Diamox) 500 mg, thymoxamine 0·5 per cent, and pilocarpine 2 per cent were given. If, after 2 h the IOP had not risen significantly, pilocarpine 2 per cent was instilled at half-hourly intervals. Subsequently, slides were projected and P/C* ratios calculated.

Another 41 eyes from 41 patients were provoked with pilocarpine and phenylephrine because the contralateral eye had had either an acute attack of CAG or a positive provocative test with pilocarpine and phenylephrine. These eyes form part of a larger series, details of which will be published separately; their inclusion in this paper depends upon the fact that the results of the provocative tests using pilocarpine and phenylephrine were negative. The 41 eyes were re-provoked with tropicamide 0·5 per cent using the methods described above.

Results

Of the 20 eyes which had a positive result when provoked with pilocarpine and phenylephrine simultaneously (P and P), eight developed CAG on re-provocation with tropicamide (T); 12 had negative results. For the purposes of this paper the significant measurement is the P/C ratio at which AC occurred or, if the result of the provocative test was negative, the maximum P/C ratio that was attained. This gives four P/C ratios:

1. The P/C ratio in P and P positive eyes at the time of AC; these eyes subsequently had a positive result with T (eight eyes, Table I)
2. The P/C ratio in P and P positive eyes at the time of AC; these eyes subsequently had a negative result with T (12 eyes, Table I)
3. The P/C ratio in P and P positive eyes which subsequently had a positive result with T—that is, the P/C ratio at which AC occurred with T (eight eyes, Table II)
4. The P/C ratio in P and P positive eyes which subsequently had a negative test with T—that is, the maximum P/C ratio attained on provocation with T (12 eyes, Table II).

Of the 41 eyes at risk of developing AC which had a negative provocative result with P and P, nine subsequently developed AC on re-provocation with T; 32 results were negative. This again gives four P/C ratios:

1. The maximum P/C ratio during provocative testing with P and P in eyes which subsequently developed a positive result with T (nine eyes, Table I)
2. The maximum P/C ratio during provocative testing with P and P in eyes which subsequently developed a negative result with T (32 eyes, Table I)
3. The P/C ratio in T positive eyes at the time of AC which had previously had a negative result with P and P (nine eyes, Table II)
4. The maximum P/C ratio in T negative eyes which had previously had a negative result with P and P (32 eyes, Table II).

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*P and C = pupillary and corneal diameter in the horizontal meridian

Address for reprints: R. Mapstone, St Paul's Eye Hospital, Liverpool L3 9PF

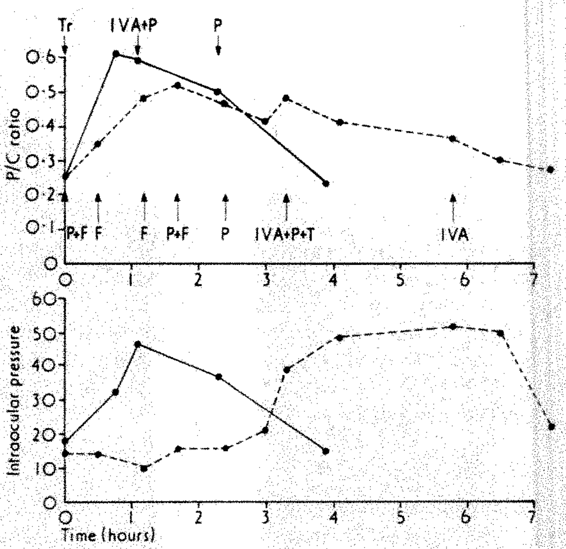

FIG. 1 *Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line)—both positive*

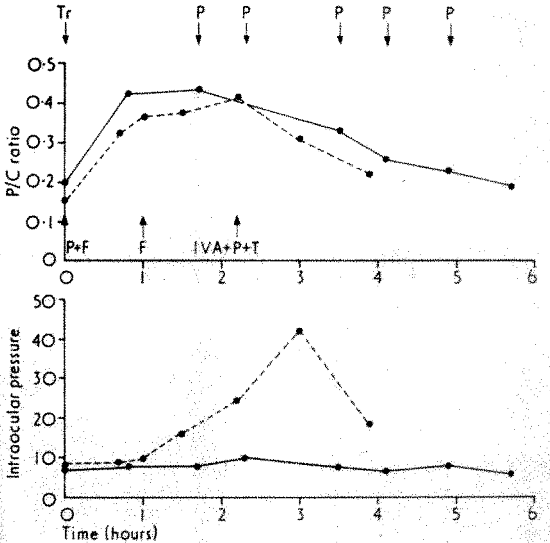

FIG. 2 *Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line)—P and P positive, T negative*

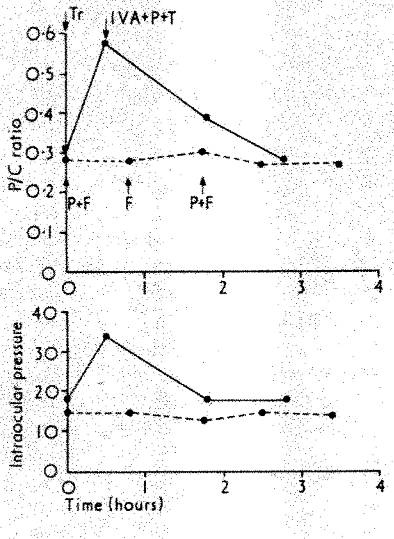

FIG. 3 *Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line)—P and P negative, T positive*

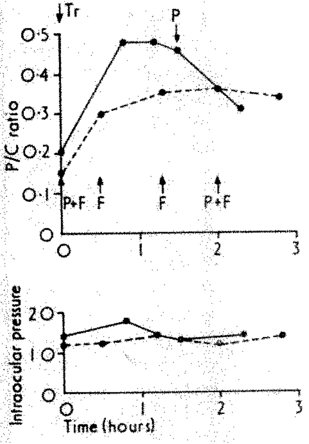

FIG. 4 *Provocative tests in same eye with simultaneous pilocarpine and phenylephrine (dotted line) and tropicamide (solid line) —both negative*

Key to Figs 1, 2, 3, and 4: F = phenylephrine; IVA = intravenous acetazolamide; P = pilocarpine; T = thymoxamine; Tr = tropicamide

The mean P/C ratios are shown in Tables I and II, and examples of results of provocative tests in Figs 1, 2, 3, and 4 for each of the four groups.

Application of Student's *t* test to the mean P/C ratios in all possible combinations taken two at a time shows no significant difference between any two means in either Table I or Table II. However, a highly significant difference was observed (at the 1 per cent level) between *any* mean from Table I and *any* mean from Table II.

Discussion

In the interpretation of the results of provocative testing, it is assumed that equal pupillary states reflect equivalent autonomic drug delivery to the anterior segment as a whole—that is, if two groups of eyes are dosed with the *same* autonomic drug, and subsequently, there is no significant difference between their respective P/C ratios, it can be assumed that equivalent amounts of drug are present in the anterior segment. Any difference in subsequent behaviour is ascribed to differing autonomic response or to other nonautonomic factors.

It is reasonable to suppose (Table I) that in each of the four separate groups there is no signifi-

Table I *P/C ratios on pilocarpine and phenylephrine testing*

Tropicamide (subsequent)	*Pilocarpine and phenylephrine*	
	Positive	*Negative*
Positive	0·39 (8)	0·38 (9)
Negative	0·38 (12)	0·37 (32)

Table II *P/C ratios on tropicamide testing*

Pilocarpine and phenylephrine (previous)	*Tropicamide*	
	Positive	*Negative*
Positive	0·49 (8)	0·51 (12)
Negative	0·54 (9)	0·49 (32)

cant difference in the augmentation of sympathetic and parasympathetic activity. Similarly, parasympathetic activity of the separate groups is equally inhibited (Table II). There is, however, a highly significant difference between Tables I and II, largely because of the variations in parasympathetic activity—that is, angle closure occurs when the pupil diameter is significantly larger with tropicamide than with pilocarpine and phenylephrine. Four types of anterior segment therefore exist in eyes at risk of developing CAG:

1. Provocation with simultaneous P and P or T are both positive
2. P and P is positive but T negative
3. P and P is negative but T positive
4. Both P and P and T are negative. (This group will not be discussed in this paper.)

In a previous paper (Mapstone, 1974c) it was shown that sympathetic activity was not necessary for angle closure to occur, but that it might actively pull a sphincter to mid-dilatation and allow the results of parasympathetic activity to close the angle. It was also shown that, in the absence of parasympathetic activity, closed-angle glaucoma did not occur. The results show that angle closure occurs with both parasympathetic inhibition (tropicamide) and excitation (pilocarpine). It is therefore a necessary consequence that closed-angle glaucoma can result from the operation of more than one mechanism. How then can the experimental observations be related to the clinical situations in which it is known that closed-angle glaucoma can occur?

The problem essentially resolves itself into an explanation of how iris can become apposed to cornea. Theoretically and experimentally this can happen in two ways (Mapstone, 1974a, b, c), either a 'push' from behind, or a 'pull' from in front of the iris plane. Considering each mechanism separately:

1. *A 'push' from behind*

A plot of sphincter pupil block force against pupil size has the form shown in Fig. 5, and it can be seen that with a mid-dilated pupil—*however obtained*—pupil block force is at a maximum and iris stroma relaxed. Given a suitably predisposed anterior segment, *some* eyes will proceed inexorably to an acute attack if the pupil is placed in this position because of the increase in pressure in the posterior chamber. This mechanism depends upon pupil block alone, and it is unneccessary to invoke adjuvant parasympathetic or uveo-scleral effects.

2. *A 'pull' from in front*

This mechanism requires pupil block generated by a pupil in miosis or mid-dilatation, and a parasympathetically (ciliary body) induced increase in trabecular meshwork outflow. As a result a pressure deficit is produced between the anterior and posterior chambers, 'pulling' the iris on to the cornea (Mapstone, 1974c). Theoretically, uveoscleral mechanisms may also be involved.

In any one eye these two mechanisms may act separately or in combination, and can result in three main types of primary closed-angle glaucoma—namely:

A. 'PUSH' CAG

Eyes exist in which the result of provocation with simultaneous pilocarpine and phenylephrine is negative, but that with a parasympatholytic such as tropicamide is positive. The main difference between the two is that angle closure occurs with tropicamide at a pupil diameter significantly larger than with pilocarpine and phenylephrine—that is, the iris—in the presence of too much parasympa-

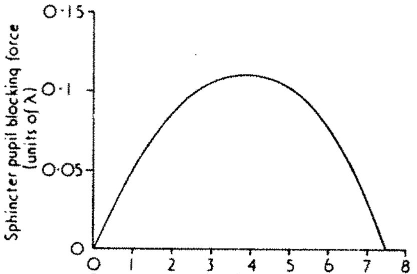

FIG. 5 *Plot of sphincter pupil blocking force (pbf) against pupillary diameter during normal pupillary play of light reflex. It can be seen that pbf is at a maximum in mid-dilatation and at a minimum when the pupil is small or widely dilated*

thetic activity—is too taut to become sufficiently *bombé* to produce AC. With tropicamide, however, the pupil dilates enough for pupil block alone to close the angle. Too much parasympathetic activity precludes AC and either sympathetic or parasympatholytic activity is necessary.

There are two conditions in which 'Push' CAG can occur:

1. Passive pupillary dilatation glaucoma (PPDG). Here parasympathetic activity is at a minimum and the experimental model is a positive dark room test or cycloplegic test. Experimentally 10 per cent of positive provocative results are in this category (Mapstone, 1976).
2. Active pupillary dilatation glaucoma (APDG). The experimental model is a positive provocative result using a sympathomimetic—for example, phenylephrine, with a mechanism similar to PPDG. The clinical counterpart is an acute attack precipitated by 'emotion', and there are many reports in the literature suggesting that this can happen. Such a proposition is difficult to substantiate, and for the moment must remain an interesting possibility.

B. 'PULL' CAG

There are eyes in which the result of provocation is positive with simultaneous pilocarpine and phenylephrine but consistently negative with tropicamide—that is, too little parasympathetic activity in the presence of pupil block is insufficient to produce CAG. Additional trabecular meshwork outflow is necessary to pull the iris on to the cornea, the two mechanisms acting synergistically.

Clinically there is a sharply demarcated group of patients in whom the history is characteristic, episodes of intermittent CAG being precipitated by parasympathetic anterior segment activity—for example, reading, knitting, and writing. The experimental model is a positive provocative reading test (Higgitt and Smith, 1955), and CAG precipitated by parasympathomimetic drugs (for example, phospholine iodide—Jones and Watson, 1967). At the termination of a reading provocative test the angle is open and the pupil mobile. It must be assumed, therefore, that during miosis sufficient of the angle is closed—temporally or spatially—for an outflow deficit to occur.

However, most patients in this category do not give such a history and it may be relevant that most intermittent and acute CAG episodes occur in the evening, after meals and at periods of quietude rather than bustle, that is, in parasympathetic man.

C. 'PUSH-PULL' CAG

Finally, eyes exist in which provocation with simultaneous pilocarpine and phenylephrine or with tropicamide both produce positive results—that is, either pupil block alone or in combination with trabecular meshwork outflow—will produce AC. Approximately 40 per cent of eyes are in this category. An example is shown in Fig. 1.

The consequences of the above findings for provocative testing and management of the contralateral eye are described in subsequent papers.

Summary

Closed-angle glaucoma is the result of two mechanisms acting either separately or in combination:

1. Pupil block creates a greater pressure in the posterior than in the anterior chamber, pushing the iris on to the cornea.
2. Increased trabecular meshwork outflow in the presence of pupil block creates a lower pressure in the anterior chamber than in the posterior, pulling the iris on to the cornea.

Three main groups of eyes manifest closed-angle glaucoma:

(*i*) Mechanism (1) is necessary and sufficient, but (2) precludes the development of angle closure.
(*ii*) Mechanism (1) is necessary but insufficient. Mechanism (2) must also be present.
(*iii*) Mechanism (1) is necessary and sufficient but (1) and (2) may combine to produce an acute attack.

I should like to thank colleagues for referring patients, Miss E. Grogan for secretarial help, and Mr R. McBride for preparing diagrams.

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Intraocular surgery in advanced glaucoma

E. J. O'CONNELL AND A. G. KARSERAS
From the Department of Ophthalmology, University Hospital of Wales, Heath Park, Cardiff

It has been found that 40 per cent of glaucomatous patients registered blind or partially sighted, are registrable when they first present for ophthalmic supervision. In addition, lens opacity contributes significantly to visual disability in registered glaucomatous patients (Miller and Karseras, 1974). Drainage procedures, and/or lens extraction, may therefore have to be considered in eyes in which visual reserves are grossly reduced from glaucomatous field loss.

There is an established view that intraocular surgery may result in obliteration of the central visual field subserving macular function when this is threatened by preoperative glaucomatous field loss. Lichter and Ravin (1974) have summarized the historical development of this view.

The present study attempts to define the incidence of postoperative loss of central vision, consequent upon modern drainage procedures and/or cataract extractions.

Material and method

A review of the case histories of glaucomatous patients who have had drainage procedures or cataract extraction was undertaken. Those patients whose preoperative

Address for reprints: A. G. Karseras, FRCS, University Department of Surgery, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN

Table I *Quadrantic nasal field loss ± arcuate scotoma*

Preoperative status						*Postoperative status (after 6 months)*			
Patient	*Visual acuity*	*Intraocular pressure (mmHg)*	*Visual field*	*Lens opacity*	*Operation*	*Corrected visual acuity*	*Intraocular pressure (mmHg)*	*Macular function*	*Lens opacity*
1	6/9	30	Upper nasal quadrantanopia Lower arcuate defect	–	Iridencleisis	6/9	22	No change	–
2	6/9	32	Lower nasal quadrantanopia	–	Scheie	Counting fingers corrected to 6/9 (see comment)	35	No change (see comment)	+
3	6/18	34	Upper nasal quadrantanopia Lower arcuate defect	+	Trabeculectomy	6/18	10	No change	+
4	6/6	28	Upper nasal quadrantanopia	–	Scheie	6/6	15	No change	–
5	6/6	50	Lower nasal quadrantanopia	–	Trabeculectomy	6/6	15	No change	–
6	6/6	28	Upper nasal quadrantanopia	–	Trabeculectomy	6/6	18	No change	–
7	6/6	30	Upper nasal quadrantanopia	–	Trabeculectomy	6/6	21	No change	–
8	6/18	30	Lower nasal quadrantanopia	+	Trabeculectomy	6/18	29	No change	+
9	6/9	40	Lower nasal quadrantanopia	–	Trabeculectomy	6/9	13	No change	–
10	6/9	28	Upper and lower quadrantanopia (nasal hemianopia)	+	Trabeculectomy	6/9	14	No change	+
11	6/9	60	Upper nasal quadrantanopia	–	Scheie	6/9	8	No change	–
12	6/9	30	Upper and lower quadrantanopia (nasal hemianopia)	–	Trabeculectomy	6/9	14	No change	–
13	6/6	38	Upper nasal quadrantanopia	–	Trabeculectomy	6/6	14	No change	–
14	6/24	40	Upper hemianopic defect (nasal and temporal)	–	Trabeculectomy	6/36	14	No change	–
15	6/9	48	Upper and lower quadrantanopia (nasal hemianopia)	–	Iridencleisis	6/9	14	No change	–
16	6/6	22	Upper nasal quadrantanopia	–	Iridencleisis	6/6	15	No change	–
17	6/9	28	Upper nasal quadrantanopia	–	Trabeculectomy	6/9	14	No change	–
18	6/12	32	Upper nasal quadrantanopia	–	Trabeculectomy	6/12	20	No change	–
19	6/18	32	Upper nasal quadrantanopia	++	Trabeculectomy	6/18	9	No change	++
20	6/60	40	Upper and lower quadrantanopia (nasal hemianopia)	++	Trabeculectomy	<6/60	16	No apparent change	++
21	6/6	22	Upper nasal quadrantanopia with lower arcuate	–	Trabeculectomy	6/6	15	No change	–
22	6/36	30	Upper nasal quadrantanopia	++	Trabeculectomy	6/36	20	No change	++

field loss encroached on central fixation were selected for this study. They were divided into two groups:

1. 24 eyes with a residual central island, with or without a temporal island of vision
2. 22 eyes in which an arcuate scotoma not only approached to within 5° of central fixation but had extended to the peripheral field to cause a nasal quadrantic defect.

An additional arcuate scotoma was occasionally present. Five patients from Group 1 and three from Group 2 subsequently had cataract extractions. Five eyes in three patients who presented with coincidental cataract and late glaucoma also underwent cataract extraction. An analysis of the results of these 13 cataract extractions was undertaken.

Preoperative and postoperative data recorded in both groups included visual acuity, intraocular pressure, Goldmann perimetry, an assessment of lens opacity, and the drainage procedure undertaken.

Postoperative data from both groups were recorded 6 months from the day of surgery. Loss of fixation after such an interval was not considered attributable to the drainage procedure. The present status of each patient was ascertained and any change of status after 6 months was recorded.

The postoperative status of the cataract group (Table III) was assessed 2 months after extraction when the eyes were free from postoperative inflammation. Loss of fixation directly attributable to the operation was therefore recorded but possible medium or long-term postoperative maculopathy was not excluded in some instances (Table III). The visual acuity of each patient at the final review was recorded.

Final review		
Time (yr)	*Visual acuity (operated eye*)*	*Comments*
4 2/12	Counting fingers 6/9*	Left cataract extraction at 15/12
1½	6/12* 6/6	Postoperative loss wrongly attributed to loss of visual field Right cataract extraction at 1 yr (vitreous loss)
2	6/18* 6/18	Bilateral lens opacities
6/12	6/6* 6/6	Patient died at 6/12
1	6/6* 6/6	—
2 3/12	6/6* 6/6	—
2 3/12	6/6 6/6*	—
1 9/12	6/9 6/24*	Slight increase in cataract
2	6/5 6/24*	Development of cataract
6/12	6/36 6/9*	Left corrected lenticular myopia
2 4/12	6/9* 6/9	—
1 10/12	6/12 6/9*	—
1 10/12	6/6 6/6*	—
1 3/12	6/36* 6/4	Atypical field loss and visual acuity preoperatively
7 7/12	6/9* 6/9	—
3½	Hand movements 6/18*	Lens opacity developing
1 2/12	6/9* Counting fingers	—
1½	6/12* 6/6	Branch vein occlusion (right)
1 2/12	6/12 6/36*	Increasing cataract
11/12	Hand movements* No perception of light	Macular function could not be assessed as patient refused lens extraction
6/12	6/6 6/6*	—
1½	6/12 6/60*	Preoperative lens opacity increasing

Preoperative field analysis in the cataract extraction group (Table III), Patients 1 to 8, was carried out several months, and in some instances years, before extraction, when the visual acuity and amount of lens opacity allowed accurate Goldmann perimetry. Patients 9–13, because of gross cataract and glaucoma at presentation, did not have perimetry. Visual fields were assessed by confrontation to hand movement and perception of light.

The difficulty in assessing macular function in the presence of cataract and a glaucomatous nasal quadrantic or hemianopic field defect is discussed later.

Results

Table I shows that drainage operations on eyes with quadrantic field loss did not lead to any further loss of visual field involving macular fixation.

In Patient 2 the visual acuity fell from 6/9 to counting fingers immediately postoperatively. This was found to be due to lenticular myopia which, when corrected, restored the visual acuity to its preoperative level. Nuclear sclerosis developed after 6 months, but cataract extraction at 1 yr, although complicated by vitreous loss, restored the visual acuity to 6/9 (Table III, Patient 7).

The only instance in which the preoperative visual acuity of 6/18–6/24 could not be explained by any condition other than glaucomatous field loss was that of Patient 14. The sequence of field loss in this patient was also unusual, in that temporal field loss, giving an altitudinal hemianopia, succeeded a nasal quadrantanopia instead of the more usual development of a nasal hemianopia.

Table II illustrates that drainage operations on eyes with central islands of vision did not cause an obliteration of macular function from extension of visual field loss. There is a higher morbidity affecting visual acuity than in the quadrantic field loss group, and losses in visual acuity therefore occurred in nine out of 24 eyes immediately postoperatively. In Patients 5, 12, and 22 the cause was first attributed to loss of central field, but later to the presence of a correctable lenticular myopia. When cataract became apparent, subsequent extraction restored the visual acuity to the pre-drainage level (Table III: Patients 4, 2, and 5).

Patient 15 was considered to belong to this group but refused operation. It was first thought that Patient 17 had lost central fixation, but the study revealed a divergent squint with a facultative suppression of the preoperative vision. Three weeks' postoperative occlusion (for shallow an-

Table II *Residual central island ± temporal island*

Preoperative status						*Postoperative status (after 6 months)*			
Patient	*Visual acuity*	*Intraocular pressure (mmHg)*	*Visual field*	*Lens opacity*	*Operation*	*Visual acuity*	*Intraocular pressure (mmHg)*	*Macular function*	*Lens opacity*
1	6/18	44	Central island	+	Trabeculectomy	6/18	18	No change	+
2	6/36	32	Central island	++	Trabeculectomy	6/36	9	No change	++
3	6/6	42	Central island and temporal island	–	Scheie	6/6	50	No change	–
4	6/12	44	Central island	–	Scheie	6/18	18	No change	+
5	6/9	29	Central island	–	Scheie	Counting fingers	25	No change (see comment)	++
6	6/6	60	Central island and temporal island	–	1. Stallard 2. Scheie	Counting fingers	20	Lost central island	–
7	6/18	42	Central island and temporal island	+	Iridencleisis	6/18	9	No change	+
8	6/12	48	Central island	–	Iridencleisis	<6/60	8	Gross reduction in macular function	–
9	6/12	30	Central island	+	Scheie	6/60	18	Gross reduction in macular function	++
10	6/6	70	Central island	–	Iridencleisis	6/6	13	No change	–
11	6/24	24	Central island	+	Trabeculectomy	6/24	17	No change	+
12	6/6	31	Central island	–	Scheie	6/24	17	No change (see comment)	++
13	6/18	28	Central island	+	Trabeculectomy	6/24	18	No change	++
14	6/9	44	Central island	–	Iridencleisis	6/9	18	No change	–
15	6/9	42	Central island and temporal island	–	Stallard	6/18	18	No change	++
16	6/9	50	Central island and temporal island	–	Scheie	Hand movements	18	Reduction of macular function	+
17	6/9	44	Central island	–	Scheie	6/9	20	No change	–
18	6/24	62	Central island and temporal island	+	Trabeculectomy	6/24	15	No change	+
19	6/18	24	Central island	+	Trabeculectomv	6/18	14	No change	+
20	6/9	28	Central island	–	Trabeculectomy	6/9	14	No change	–
21	6/6	46	Central island	–	Trabeculectomy	6/6	18	No change	–
22	6/9	34	Central island	–	Scheie	6/60	21	See comment	++
23	6/6	44	Central island and temporal island	–	Trabeculectomy	6/6	26	No change	–
24	6/9	40	Central island and temporal island	–	Iridencleisis	6/12	23	No change	+

terior chamber), a lack of binocular field available for fusion, and a possible pre-existent exophoria may have contributed to this status.

In three instances there was an irreversible loss of visual acuity – due to a postoperative maculopathy (Patient 16), exacerbation of a preoperative maculopathy (Patient 8), and a maculopathy which developed coincidentally with a cataract postoperatively, or subsequent to an eventual cataract extraction (Patient 9, Table II; Patient 1, Table III).

After two unsuccessful drainage procedures with very raised intraocular pressures Patient 6 lost central fixation, and it is not certain whether the surgery or the uncontrolled pressure was the cause.

Patient 7 lost central vision 2 years after the drainage procedure.

Table III shows that cataract extraction did not lead to worsening of central vision. Three patients out of the 13 did not obtain an improved visual acuity. In Patients 1 and 9 this was due to maculopathy and in Patient 12 to absence of macular function. Maculopathy also restricted visual improvement to 6/18 in Patient 8.

Of the five eyes (1 to 5) with an isolated central visual field, four (2 to 5) survived a drainage procedure and a cataract extraction allowing visual acuities of 6/9. In Patient 1 a coincidental maculopathy restricted vision to the preoperative level of perception of light.

The three (Patients 6–8) with charted pre-extraction quadrantic defects did not lose central fixation after a cataract extraction or a preceding drainage operation.

The five eyes (9 to 13) belonged to three patients

Final review

Time (yr)	*Visual acuity (operated eye*)*	*Comments*
1	6/9 6/18*	—
1 3/12	6/12* 6/36 (lens opacity and quadrantic loss of visual field)	Cataract extraction at 1 yr Prefers to function with aphakic central island
3½	6/6* 6/5	Stallard procedure 3/12 before Scheie
Died at 8/12		Preoperative maculopathy
10	6/18* 6/9	Cataract extraction at 1 yr Bilateral aphakia, loss of fixation originally diagnosed
3 4/12	Hand movements* 6/9	5 wk between the 2 operations with intraocular pressure 50 mmHg Flat anterior chamber and choroidal detachment after Scheie
4 3/12	Hand movements* 6/5	Central vision loss at 2 yr Gradual deterioration
1 3/12	Counting fingers counting fingers*	Progressive maculopathy in both eyes Pathological myopia
[illegible]	Perception of light* 6/36	Cataract extraction at 2½ yr showed gross maculopathy
3½	6/6* 6/9	—
1½	6/18 6/60*	Increase in cataract
2 3/12	6/9* counting fingers	Cataract extraction at 1 yr Patient functioning with aphakic central island
2 8/12	6/60* 6/36	Bilateral lens opacities
2	6/6 6/9*	—
3 3/12	6/36* hand movements	Increasing lens opacities
3 3/12	6/36 hand movements*	Postoperative exudative maculopathy
2	6/9* 6/9	Divergent squint with suppression Difficulty in locating test type
2 3/12	6/9 counting fingers*	Progressive lens opacities
1½	6/18* 6/60	—
6/12	6/12 6/9*	—
6/12	6/12* 6/9	—
4	6/9* 6/12 (aphakic)	Cataract extraction at 1 2/12 yr
7/12	6/6* 6/9	—
4	Counting fingers* 6/6 (aphakic)	Progressive cataract both eyes Cataract extraction at 3 yr

who presented with both advanced glaucoma and cataracts. Intraocular pressures were controlled medically before extraction in three eyes (Patients 9, 10, and 11) and by peripheral iridectomy and medical treatment in two (Patients 12, 13).

Considerable improvement in visual acuity resulted in eyes 10, 11, and 13. The postoperative development of maculopathy in Patient 9 allowed only the preoperative vision of 6/60.

Patient 12 was the only example in the present series in which macular function was lost before the development of a nasal hemianopia. This patient had chronic angle-closure glaucoma with intraocular pressures of 60 mmHg at presentation. Central fixation was absent postoperatively. In Patients 8 to 12 macular function could not be demonstrated preoperatively.

DRAINAGE OPERATIONS AND CATARACT FORMATION IN ADVANCED GLAUCOMA

Within 6 months, in the 'central island' group of 24 patients, postoperative lens opacities significantly reduced vision in five patients (Table II, Patients 5, 9, 12, 15, and 22). After the period of final review cataracts had progressed in a further five patients (Patients 2, 11, 13, 18, and 24). Preoperative lens opacities were present in four of those 10 patients (Patients 2, 11, 13, and 18). In the four Scheie operations the cataracts developed within 6 months and were not associated with preoperative lens opacities. In the four trabeculectomies there were preoperative lens opacities and these progressed significantly after the 6-month interval.

Within 6 months, in the 'quadrantic loss' group of 22 patients, postoperative lens opacities significantly reduced vision in one patient (Table I, Patient 2) and this was corrected to 6/9. After the period of final review cataracts had progressed in a further eight eyes (Patients 1, 8, 9, 10, 16, 19, 20, and 22). Preoperative lens opacities were present in five of these eyes.

Consideration of both groups (Tables I and II) shows that 10 out of 25 trabeculectomies resulted in the progression of lens opacities, but that preoperative opacities were present in nine of these.

Five out of 12 Scheie operations were associated with progressive postoperative cataract and preoperative lens opacity was present in one instance. Inequality of follow-up does not allow valid comparison between the Scheie and trabeculectomy procedures, but at the 6-month level, trabeculectomy would appear to induce less deterioration of visual acuity of lenticular origin.

Discussion

Lichter and Ravin (1974) correctly stated that many of the opinions regarding loss of central vision in late glaucoma after intraocular surgery are the result of clinical impression rather than of the study of a series of patients. It is of interest to analyse the relatively few series which have led to a reluctance to undertake intraocular surgery in advanced glaucoma.

Bloomfield and Kellerman (1949) compared the results of surgery in 19 patients with those of medical treatment in 22 patients. All had residual central islands and after an average follow-up period of 2 years and 4 months it was found that vision was better maintained in the unoperated group. The cause of reduction in visual acuity was not determined so that reversibility of the condition was not excluded.

The present study showed that postoperative

Table III *Cataract extraction group*

Preoperative status				*Postoperative status (2 months)*		
Patient	*Corrected visual acuity*	*Intraocular pressure (mmHg)*	*Visual field*	*Corrected visual acuity*	*Intraocular pressure (mmHg)*	*Macular function*
1	Perception of light	8	Central island with temporal island	Perception of light	18	See comment
2	6/36	17	Central island	6/9	16	Maintained
3	Hand movements	5	Central island	6/9	16	Maintained
4	Counting fingers	25	Central island	6/9	18	Maintained
5	Counting fingers	21	Central island	6/9	15	Maintained
6	6/36	22	Upper nasal quadrantanopic loss with lower arcuate defect	6/6	24	Maintained
7	Counting fingers	30	Lower nasal quadrantanopic defect	6/9	8	Maintained
8	6/60	18	Upper nasal quadrantanopic defect	6/18	21	Partially maintained
9	6/60	17	Lower nasal quadrantic defect	6/60	16	See comment
10	Hand movements	20	Upper and lower quadrantic defects (nasal hemianopia)	6/12	20	Maintained
11	Counting fingers	24	Nasal hemianopia	6/12	20	Maintained
12	Counting fingers	21	Upper nasal quadrantic defect	Counting fingers	20	Absent (? lost from extraction)
13	6/60	32	Upper nasal quadrantic defect	6/9	15	Maintained

refractive error and cataract formation accounted for the loss of visual acuity postoperatively in four out of 10 patients (Table II). Only five out of the total of the 24 central island group had significant irreversible reduction of vision, up to the time of the final review (Table II, Patients 6 to 9, 16).

The trephine operations and the acknowledged inexperience of some surgeons would have increased the reversible postoperative loss of acuity in Bloomfield and Kellerman's series. The amount of irreversible macular loss in uncontrolled medically-treated patients would also increase with a follow-up longer than the 2 years averaged.

Nemetz and Papapanos (1959) found that visual acuity was the most significant factor influencing the results of surgery. Thus only 6 per cent of 212 eyes with a preoperative vision of more than 6/60 'turned blind' after operation and 64 eyes with a preoperative vision of 6/60 or less had an incidence of 64 per cent blindness. All patients had a 'contraction of the visual field as low as 5° in one quadrant'.

Glaucomatous field loss does not significantly reduce the visual acuity unless it extends to inside the 5° isoptre (see below). In the series of Nemetz and Papapanos it is likely that macular fixation was involved preoperatively in most of the 64 eyes or that there was a non-glaucomatous cause for the preoperative vision of 6/60 or less. These eyes therefore cannot be said to have lost central

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Final review		
Time (yr)	*Visual acuity (operated eye*)*	*Comments*
6/12	6/6 Perception of light* (aphakic)	Large white scar at macula observed postextraction Drainage procedure 2½ yr before extraction
1 2/12	6/9 counting fingers	Drainage procedure 1 yr before extraction Functioning well with aphakic central island
7/12	6/12* 6/36 (phakic)	Drainage procedure 1½ yr before extraction Patient prefers to function with aphakic central island
9	6/18* 6/9	Drainage procedure 1 yr before extraction Bilateral aphakia
3	6/9* 6/12 (phakic)	Drainage procedure 1 2/12 yr before extraction Difficulty in locating test chart but eye is unused, being held in reserve
[illegible]	6/9* counting fingers	Drainage procedure 1 3/12 yr before extraction Functioning well with aphakic eye
6/12	6/12* 6/6 (phakic)	Drainage procedure 1 yr before extraction Operated eye held in reserve Vitreous loss
7/12	6/18* counting fingers	Maculopathy evident postoperatively Patient died at 9/12
1 3/12	6/18 6/60*	Progressive maculopathy reduced visual acuity of 6/24 to 6/60
1 2/12	6/12* 6/24	Cyclodialysis 3/12 postoperatively Bilateral aphakia.
2 8/12	6/12 6/24*	Slight membrane over pupil Visual acuity transiently 6/12 Macula function not thought to be present preoperatively but patient insisted on extraction in view of result of first operation (Patient 10) Normal visual functioning
9/12	6/12–6/18 counting fingers*	Iridectomy before extraction (subacute angle closure) Macular function could not be demonstrated in early stages of cataract
1 9/12	6/12–6/18* counting fingers	Iridectomy 1 yr before extraction (subacute angle closure) Visual functioning much improved

fixation as it is unlikely to have been present preoperatively.

Fanta and Herold (1966) undertook static perimetry before and after operation on 10 eyes in which the macular fixation was approximated by glaucomatous field loss. They demonstrated a fall in the profile of sensitivity to static perimetry and a reduction of the functioning field in all instances. However, fixation was maintained in eight of their cases. Of the two who lost fixation, one was a high myope (Case 10). In the other (Case 8), the inferior scotoma, almost splitting fixation preoperatively, was questionably glaucomatous as it was atypical in shape and crossed the horizontal meridian nasally. Fanta and Herold suggested that operation was justified only if the limits of the visual field did not encroach more than 5° from fixation and that loss of fixation was probable if the encroachment was 3° or less.

This supposition is not borne out by the recent results of Lichter and Ravin (1974) or those of the present series. We found that the patients' response to perimetry inside the 5° isoptre is usually inconstant and that the actual visual acuity is the best method of determining macular involvement in glaucomatous field loss in these circumstances. We found that acuity fluctuated at different examinations, usually between 6/9 and 6/18 and, exceptionally, 6/24 (Patient 14, Table II).

Careful refraction and time for the patients' concentration and orientation of visual direction were the most important factors in eliciting the maximum visual acuity. When fixation is involved the acuity is invariably less than 6/60 and when the condition is due to glaucomatous field loss the decline to this level is dramatic unless other factors such as cataract have already lowered the acuity to between 6/24 and 6/60.

Lichter and Ravin (1974) attempted to classify late glaucoma in terms of visual acuity and field loss. They did not give a full description of the visual fields but in 23 eyes in which visual field loss 'involved fixation' (as shown by a reduced visual acuity), and in nine eyes in which field loss extended to within 5° of fixation, drainage procedures did not influence macular function. Loss of acuity was attributed to cataract and this caused a similar loss of acuity postoperatively in glaucomatous eyes in which fixation was not threatened.

The present investigation has also revealed that postoperative cataracts reduce the visual acuity. They occurred earlier, and with a greater effect on vision, in the central island group than in the nasal field defect group. This may mean that the more severe the glaucomatous damage, the more vulnerable are the eyes to postdrainage cataract formation. Alternatively, the 'tunnel' vision of these eyes may be more vulnerable to minor lens opacities. The number of trabeculectomies carried out was also much lower in the central island group, and this operation appears to be much less likely to cause postoperative lens opacity, at the 6-months level of follow-up.

Lichter and Ravin's series was remarkable because of the absence of any postoperative maculopathy. In the central island group (Table II) in the present series maculopathy reduced vision postoperatively in three out of 24 eyes (12·5 per cent). Postoperatively maculopathy was not seen in the nasal field defect group. It appears from this series that the central island group is more vulnerable not only to postoperative cataract formation, but also to postoperative maculopathy. Of a total of 46 drainage procedures (Tables I and II), however, maculopathy developed in three eyes (7 per cent).

Lawrence (1969) found a similar postoperative morbidity regarding cataract and maculopathy. In 19 eyes with residual central islands, central fixation was not lost but visual acuity was reduced as a result of cataract in six eyes and maculopathy in one. In 24 eyes with 'quadrantic' field loss, central fixation was maintained but vision was reduced by cataract in seven eyes and by macular degeneration in eight. All were eyes which had been trephined and this operation would appear to cause a greater postoperative morbidity.

Kronfeld and McGarry (1948) found that, in 18 eyes with field defects extending to within 5° of fixation (mainly central islands), 95 per cent retained fixation for 5 years postoperatively. Immediate postoperative loss of fixation was not recorded. Twelve eyes with similar field defects, uncontrolled medically, were not operated upon and nine (75 per cent) retained fixation during 5 years. Although their study supports the view that surgery does not significantly affect fixation, it does call into question the wisdom of surgery in elderly patients with advanced glaucoma in whom pressures are not greatly raised or have been reduced significantly by medical therapy.

The present series has shown that the risk of reoperation for cataract in the 'quadrantic loss' and the central island groups is in the order of 30 per cent within the periods of final review. The risk of a maculopathy for the residual central island group is in the region of 12·5 per cent within 6 months (Tables I and II).

If the 5-year survival of macular function is improved only from 75 to 83 per cent by drainage surgery (Kronfeld and McGarry, 1948), these sequelae of surgery would not be justified. However, Kronfeld and McGarry did not describe the amount of lowering of intraocular pressure achieved medically in their unoperated group and this may have more significance regarding survival of the visual field than 24-hour control under the arbitrary pressure of 21 mmHg (Miller and Karseras, 1974). In cases in which medical therapy has little therapeutic effect on high intraocular pressures and reasonable longevity is assumed, the risks of surgery may be considered to be justified in patients with advanced glaucoma.

The results of cataract extraction show that 10 of 13 patients had an improved visual acuity, maculopathy being responsible for postoperative morbidity in three patients.

Lawrence (1969) carried out eight cataract extractions in eyes with macular function and this was retained in six patients (three central islands and three quadrantic loss). Maculopathy restricted visual improvement in two eyes with quadrantic field loss.

These findings suggest that cataract extraction in eyes with advanced glaucoma will usually incur benefit to the patient and that the risk of removing the small amount of sight the patient may have, is small (reduction or loss of visual acuity was not recorded in the present series or in Lawrence's eight cases). Failure to improve the vision may occur in 24 per cent of patients (five out of 21 extractions, combining data of Lawrence and present series), mainly due to an increased incidence of maculopathy. Sixteen of these eyes were subjected to drainage operations before cataract extraction. Both series show the development of a postdrainage maculopathy in some of these patients with late glaucoma, so that the culpability of the cataract extraction itself may be less.

In the monitoring of glaucoma simplex a gradual progressive loss of visual acuity is frequently observed. This gradual loss is not due to glaucomatous field loss (despite apparent changes in perimetric field analysis), but often to progressive lens opacity. We have found that, as in retinitis pigmentosa with residual macular function, minor lens opacities severely affect visual acuity in late glaucoma. When loss of visual acuity is severe enough lens extraction will improve the sight in over 75 per cent of patients. Six of the 11 patients who underwent cataract extraction experienced a great improvement in visual function (Table III; Patients 2, 3, 6, 8, 10, and 13). Two aphakic eyes (4, 11) are contributing to binocularity, and two (5, 7) are held in potentially useful reserve.

When cataracts develop in patients with glaucoma simplex who are under ophthalmic care their management is easier. The history of the visual acuity and the visual fields will usually indicate if macular function is likely to be present, as discussed already.

When patients present with advanced cataracts and late glaucoma (Patients 9 to 13, Table III) it may be impossible to determine the status of macular function. Thus in four of these five patients, pinhole vision, Maddox rod testing, entoptic imagery, and testing the perception of two approximated coloured lights did not indicate the presence of macular function. Perimetric field analysis is too refined a technique to determine the visual fields. If vision is capable of registering hand movements this visual stimulus to confrontation in the four quadrants has been found to be the most useful in determining the extent of glaucomatous field loss. If visual fields are full to confrontation macular function is invariably present despite possible central Bjerrum scotoma. It is rare for central vision to be lost subsequent to a quadrantic defect (Patient 12, Table III) and it is often retained in the presence of a nasal hemianopic defect (Table III, Patients 10 and 11). Such glaucomatous field defects, when associated with advanced cataract, do not preclude potential macular function. This was attained in three out of five eyes in these circumstances (Table III, Patients 10, 11, 13). It is rare to make such patients' vision worse, so that reversibility of visual loss may be excluded by cataract extraction when the patient's binocular visual status and life situation merit it.

Summary

Loss of visual field subserving macular function has been found to be rare after intraocular surgery in advanced glaucoma. Abrupt changes in refractive error, lens opacity, and suppression must be carefully excluded before macular fixation is deemed lost.

Out of 69 intraocular procedures (46 drainage operations, 13 cataract extractions) two patients lost central visual field subserving macular fixation possibly as a result of surgery.

There is an increased incidence of postoperative maculopathy in late glaucoma. Three drainage operations out of 46 and four cataract extractions out of 13 had this complication.

Altogether 30 per cent of drainage procedures induced deterioration of visual acuity of lenticular origin to a level normally requiring cataract extraction. Trabeculectomy was found to be less likely to cause this sequela than the Scheie procedure at the 6 month postoperative stage. However, 77 per cent of patients with advanced glaucoma and cataract obtained a satisfactory improvement in visual status after cataract extraction.

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Influence of thymoxamine on changes in pupil diameter and accommodation produced by homatropine and ephedrine

SUSAN SMALL AND J. H. STEWART-JONES
From the Department of Ophthalmic Optics and Visual Science, City University, London
AND
P. TURNER
From the Department of Clinical Pharmacology, St Bartholomew's Hospital, London

Thymoxamine is an α adrenoceptor blocking drug which has miotic actions when applied topically in the eye (Sneddon and Turner, 1968; Turner, 1969). It has been recommended for reversal of the potent mydriatic effect of a combination of eucatropine and phenylephrine (Smith, 1971). Since several types of mydriatic agents are used clinically, a study has been carried out to investigate the miotic effect of thymoxamine after treatment with homatropine and ephedrine separately and in combination.

Material and methods

Twelve healthy students (six men, six women), aged 19–21 years, and with various eye colours volunteered for the investigation. Each was subjected at weekly intervals, in random order based on three Latin square designs, to four different treatments shown in Table I. Before instillation of any drug into the conjunctival sac, the pupil diameter was measured using a clear Perspex pupillometer in which holes of various sizes were drilled for direct comparison with the subject's pupil and which measured pupil diameter to the nearest 0·5 mm. Uniocular amplitude of accommodation was recorded for both eyes using a Duane near-point rule, the other eye being occluded. The mydriatic agent or saline was then instilled into both eyes, and at 30 min thymoxamine 0·1 per cent was instilled into the right eye. Pupil size was recorded at 30 min after the start of the experiment just before instillation of thymoxamine and then at 15 min intervals until 90 min. The amplitude of accommodation was recorded at 30, 60, and 90 min. Illumination was kept constant in the laboratory throughout the investigation.

Results

The mydriatic effects of the treatments used, their reversal by thymoxamine, and the changes in amplitude of accommodation are shown in the Figure. The statistical analyses of differences between the eyes in pupil diameter and amplitude of accommodation at 90 min using a paired Student's t test are given in Table II.

After treatment with saline, thymoxamine produced the expected miosis in all subjects. It also

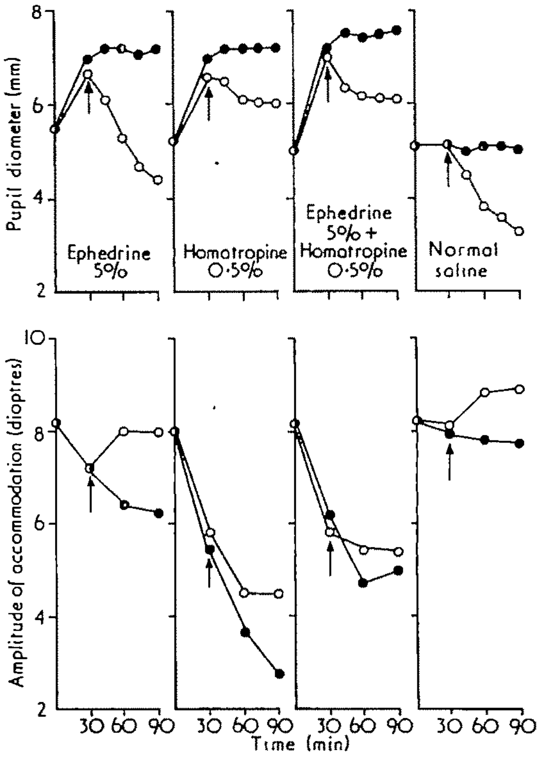

FIGURE *Changes in pupil diameter and accommodation produced by normal saline, ephedrine, and homatropine alone and in combination, instilled into both eyes at zero time and observed over 90 min (●-●) and their modification by thymoxamine (O-O) instilled into one eye at 30 min (↑), in 12 subjects*

Address for reprints: Professor P. Turner, Department of Clinical Pharmacology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE produced a small but significant increase in amplitude of accommodation compared with the opposite untreated eye. The mydriasis induced by ephedrine was completely reversed by thymoxamine. A small but significant reduction in accommodation was found after ephedrine, and this was also reversed by thymoxamine. Thymoxamine failed to reverse completely at 90 min the mydriasis produced by homatropine, nor did it reverse completely the reduction in amplitude of accommodation produced by homatropine. Similar results were obtained with the combination of ephedrine and homatropine. The mydriasis produced by the combination was significantly greater ($P < 0{\cdot}01$) than that produced by homatropine alone. All treatments were well tolerated. In particular, thymoxamine in the concentration of 0·1 per cent produced no irritation, giving less discomfort than ephedrine 5 per cent.

Discussion

These results confirm those of Smith (1971) that thymoxamine eye drops quickly reduce the mydriasis produced by a combination of an anticholinergic drug with a sympathomimetic amine. The reversal is not complete, however, for the sympathetically mediated dilator pupillae component plays a smaller part in the mydriasis than reduction of the parasympathetically mediated sphincter pupillae component (Mapstone, 1970).

This is further demonstrated by the very small, although statistically significant, difference between the mydriasis produced by homatropine alone and that by its combination with ephedrine. This has important implications in other situations in which patients may be treated with drugs possessing anticholinergic properties. For example, Ghose, Dobree, Taylor, and Turner (1974) showed that the miotic effects of thymoxamine and of guanethidine are reduced in patients receiving amitriptyline, a tricyclic antidepressant drug, probably because of its anticholinergic activity. While it is possible that a higher concentration of thymoxamine such as 0·5 per cent would have produced a greater miosis in the present study, it causes marked irritation in many subjects, and cannot be recommended for routine use.

While it is generally reported that ephedrine does not cause cycloplegia, these results show that ephedrine 5 per cent produced a small but statistically significant reduction in accommodation, and so confirm the observations of Howard and Lee (1927) and Mitchell (1959) that ephedrine 1–10 per cent produced a fall in accommodation of 0·25–2·50 dioptres. The increase in accommodation produced by thymoxamine is consistent with these observations. It is probable that this is associated with the changes in pupil size produced by these agents, as Campbell (1957) showed that an increase in pupil diameter was accompanied by an increase in the hyperfocal distance. Such changes must be considered when accommodation studies are performed in patients with sympathetically mediated pupillary disorders.

Table I *Mydriatic regimens employed in both eyes of 12 volunteers 30 min before instillation of thymoxamine into the right eye*

Regimen	*Drug instilled at zero time into right and left eye*
A	Ephedrine hydrochloride 5·0 per cent
B	Homatropine hydrochloride 0·5 per cent
C	Ephedrine hydrochloride 5·0 per cent and homatropine hydrochloride 0·5 per cent
D	Sodium chloride 0·9 per cent

Table II *Influence of thymoxamine 0·1 per cent on the mydriasis and change in accommodation produced after 90 min by ephedrine, homatropine, and a mixture of ephedrine and homatropine in 12 subjects*

Treatment	*Mean pupil diameter (mm)*					*Mean amplitude of accommodation (D)*				
	No thymoxamine	*Thymoxamine*	*SE diff.*	*t*	*P*	*No thymoxamine*	*Thymoxamine*	*SE diff.*	*t*	*P*
Saline	5·1	3·5	0·15	10·7	<0·001	7·9	8·9	0·45	2·29	<0·05
Ephedrine 5 per cent	7·2	4·4	0·21	13·3	<0·001	6·4	7·9	0·57	2·72	<0·02
Homatropine 0·5 per cent	7·3	6·0	0·11	11·4	<0·001	2·9	4·6	0·42	4·03	<0·01
Ephedrine + Homatropine	7·7	6·2	0·14	10·9	<0·001	5·2	5·9	0·30	2·20	<0·05

Summary

Local instillation of thymoxamine eye drops (0·1 per cent) completely reversed the mydriasis produced by ephedrine (5 per cent) but not that produced by ephedrine (5 per cent) together with homatropine (0·5 per cent). Small but significant changes in accommodation were found with ephedrine and with thymoxamine, as well as the larger expected changes with homatropine.

We thank the 12 students who participated as volunteers in this study, and William Warner & Co Ltd for supplying thymoxamine.

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Clinical assessment of rhodopsin in the eye
Using a standard fundus camera and a photographic technique

U. B. SHEOREY
From the Department of Visual Science, Institute of Ophthalmology, London

In recent years, the technique of fundus reflectometry (see Weale, 1974), has been shown to be particularly helpful in locating defects in the primary stage of the transduction of light into vision. It has thus been possible to assess the availability of retinal pigment in cases such as night blindness. When the results are considered together with those from complementary electrophysiological or psychophysical tests, a much clearer diagnosis concerning the site of the lesion is possible. The basis of the measurement is the marked change in the absorption spectrum of the visual pigment rhodopsin when it is bleached by strong exposure to light. Thus if a defined part of the retina is bleached—that is, an imprint or an 'optogram' is formed on the retina—a comparison of the reflectances of the unexposed and exposed areas can be used as an indicator of the availability of pigment in that region. The measurement can be carried out only for a double transit of light through the retinal layer provided that the bleaching of the eye has affected only the retinal pigment.

In most previous clinical studies, complex apparatus was used and the procedure was involved. We have been able to use a simple procedure and a conventional fundus camera, albeit slightly modified. The use of a standard fundus camera and a flash bleaching technique has obvious clinical advantages—for example, the co-operation required of the patient is minimal. These modifications are described in this paper and the use of this technique in assessing the pigment concentration in rod rich parts of the retina is illustrated. These modifications were designed so that they could either be easily removed from the light path in the camera or left in place provided they did not hinder the original application of the camera. As very little machining is required on the main body of the apparatus, its absence from the clinic is short. An approximate assessment of the density contrast of the optogram can be made immediately after developing and fixing the latent image on the photonegative. A value for the density contrast can be obtained later by means of a microdensitometer. The modified apparatus thus provides a simple procedure for routine and rapid clinical assessment of rhodopsin in the eye.

Method

The spectral absorption of the visual pigment is different for the bleached and the unbleached states, and the intensity of the light beam which has traversed through the retinal layer containing the pigment will be modified accordingly. We may compare the intensities either from two adjacent areas, one of which is bleached, or from a given area before and after it is bleached. If this difference is due only to a change in the retinal pigment, we can relate the changes in the concentration of that pigment to changes in optical densities. The change in optical density is a function of the wavelength of light used for the measurement; it is largest in bluish-green light for the rod pigment.

The present method uses a photographic technique to record this difference from adjacent areas of the retina after a defined part of the retina has been bleached. In order to relate the recorded density differences to true differences, the photonegative also carries a calibration which is superimposed at the same time as the recording. Thus, distortions which may be introduced during the process of the development of the latent image on the film can be compensated (Arnold, Rolls, and Stewart, 1971).

APPARATUS

The basic apparatus consists of a standard Zeiss* fundus camera and its associated electronic power supply unit for the xenon flash tube. The paths of the light beams which are used to provide the retinal illumination for general viewing, flash bleaching, and photography are unfortunately largely common. In order to produce an optogram by bleaching a defined part of the retina, an aperture in this light path is required, but it has to be removed for general viewing of the fundus and during photography.

These modifications are illustrated schematically in Fig. 1. The original tubular holder which supports the objective lens L is replaced by a modified

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Address for reprints: U. B. Sheorey, Department of Visual Science, Institute of Ophthalmology, Judd Street, London WC1H 9QS

*C. Zeiss, Oberkochen, Germany

housing. The axial length of the housing and the mechanical dimensions at both its ends are exactly the same as for the original tube so that the two can be interchanged. The housing accommodates a moveable carriage which in turn accommodates an aperture-plate. The apertures can be moved along the optical axis by rotation of the shaft S_1 so that they can be made conjugate with the patient's retina. Either aperture may be brought into the light path by means of the knob K_2. A shielded press-switch, Sw, is mounted at the end of K_2 to activate the xenon flash B_2 for retinal bleaching. This switch is wired electrically in parallel with that on the mechanical shutter of the 35 mm camera. This duplication of the switch is desirable to enable the flash to be activated independently of the camera and to reduce the number of hand movements by the operator during the procedure.

The aperture-plate P carries two apertures, A_1 for normal viewing of the retina and for photography, and A_2 for defining the retinal area that is to be bleached (Fig. 1*c*). The plate is mounted perpendicular to the optical axis of the fundus camera and in the moveable carriage. Both apertures are made from thin sheets of brass and can easily be removed and exchanged for other shapes and sizes—for example, as might be required for the investigation of the density of the retinal pigment along the vertical meridian. The aperture A_1 is currently 28 mm diameter, equivalent to a retinal view of 35°. Access to these apertures may be obtained simply by removing the lens L. All internal surfaces of this housing and the additional components which are mounted in the fundus camera are painted matt-black so as to prevent stray reflections within the camera reaching the patient's eye or the recording camera.

F_1 is the deep-red colour filter that is required in the path of the white light from the bulb B_1 to provide a safelight for retinal viewing. It is constructed from a sheet of coloured gelatine (Ilford, no. 608) which is clamped between two thin plates of glass and held within a metal plate. A rectangular slot is required in the side panel of the apparatus for the insertion or removal of the filter from the light path. Note that F_1 does not need to be handled since it does not interfere with either the bleaching or the recording steps. Two miniature light-emitting diodes* are also provided within the housing as additional fixation targets. These diodes are required because the patient cannot see the internal target T once the aperture A_1 is changed to A_2 if his centre of fixation is outside the area defined by A_2. Furthermore, since the paths of the viewing and the bleaching lights are largely common, T is not illuminated when the bluish-green filter is introduced into the light path before photography. Few people, however, have any difficulty in maintaining fixation during the brief interval required to introduce the bluish-green filter and photograph the optogram.

The safelight path is combined with the path of the xenon flash light by means of the half-mirror BS. In order to remove the infrared content of the intense xenon-flash, BS was remade from a piece of heat-absorbent glass. The bluish-green colour filter F_2, which is required during the recording of the optogram, is placed in the light path after BS. The rest position of this filter is out of the light path as it is manually pushed into place immediately before photography and then retracted. Within the same mount, neutral-density filters may also be incorporated so as to adjust the retinal illumination independently of the power supply to the flash tube. It is thereby possible to achieve a common setting for bleaching and photography, thus considerably simplifying the procedure and avoiding waiting for the electronic power supply to discharge and recharge between changes in settings.

The calibration is superimposed on the film by placing a density-graticule DG in the recess between the film and the mechanical shutter of the camera; therefore, it is only in the path of the light reflected from the fundus. A typical graticule is illustrated in Fig. 1*d*. The part of the film on which the fundus image is recorded is indicated by the broken circle; the inner rectangle indicates the position of the optogram image relative to the graticule and one frame of the film. The graticules are made by exposing a series of strips—for example, (20 mm long, 2 mm wide, spaced 2 mm apart) on to photographic paper*. For present use, the exposure time was simply varied in steps during a trial run and then the appropriate exposure times were selected so as to produce strips of optical densities in the range 0·05–0·15. The position, size, and orientation of these calibration steps are determined by the particular densitometric investigation that one wishes to perform. For example, for investigations of the changes in the pigment concentration along the vertical meridian, it would be useful to orientate these strips horizontally—that is, perpendicular to the bleaching rectangle. It is essential that an adequate calibration is recorded on the same film in the vicinity of the region of interest.

CALIBRATION OF THE FLASH SOURCE

The flux incident upon the patient's retina during the flash bleaching and photographic steps was calculated from the radiometric measurements which were taken on the xenon flash. To do so, a model eye was formed in front of lens L and a

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*Motorola, type MLED 20

*Ilford N4E50

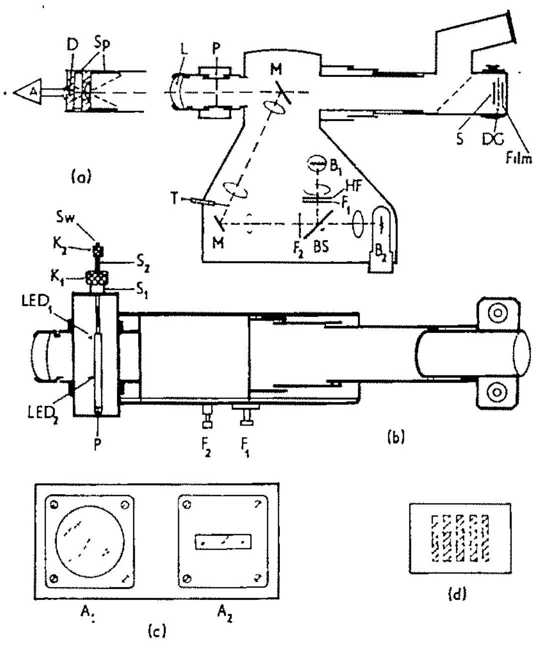

FIG. 1 (a) *Schematic side view of Zeiss fundus camera showing principal components and modifications. Tubular housing at front houses objective lens* L, *and moveable holder for aperture plate* P. *Also shown are: adjustable, internal fixation target* T; *mirrors* M; *combined heat-filter and beam-splitter* BS; *filter* F_2 *for photographic step; heat-absorbent filter* HF; *deep-red filter* F_1; *white viewing light* B_1; *xenon flash tube* B_2; *calibration graticule* DG; *camera shutter* S; *additional fixation target,* LED. *Cylindrical assembly to left of lens* L *is model eye used to measure flux arriving at simulated retinal plane. During use, assembly is pushed over mounting tube of lens* L *and distances are fixed by spacing rings* Sp. *Output of photodetector* D *is fed into amplifier* A *for measurements*

(b) *Schematic plan of modified fundus camera showing additional fixation targets* LEDs *and various control knobs and shafts. Rotation of* K_1 *moves plate holder* P *along optical axis for focus adjustments. Bleaching aperture is brought into light path by pulling* K_2 *outwards. Flash can be activated by switch* Sw. *This is electrically connected to be in parallel with that on shutter release switch of camera*

(c) *Front view of aperture plate holder* P *which carries two apertures,* A_1 *for normal viewing of fundus and* A_2 *for bleaching a defined area of fundus*

(d) *Schematic illustration of density-graticule* DG *which is placed between the shutter of camera and film so as to impress a calibration on film during photography. Broken line circle, corresponding to aperture* A_1, *indicates area within which retinal image is formed. Inner rectangular region is area, corresponding to* A_2, *within which optogram is present*

photodiode was placed within it. This assembly is shown in Fig. 1*a* to the left of the objective lens L. The lens of the model eye had a focal length of 17 mm and an aperture of 8 mm diameter. An objective radiometric method using a photodiode was used in preference to a photometric method using an eye because it is easier and more precise to use routinely in the clinic. The difficulty in making routine photometric measurements by eye with this fundus camera should be noted. The flash source is imaged in the pupil plane of the observer's eye; this image is not uniform and is almost as large as a fully dilated pupil. Furthermore, the output flux of the flash varies according to the interval between firings and the age of the tube.

The waveform of the xenon flash (measured at $\lambda=505$ nm) consisted of a fast rising front of about 0·1 ms (measured from 5 per cent of peak to the peak) followed by an exponential decay with a characteristic decay time of about 0·4 ms (from the peak to $1/e$ of the peak, where $e = 2{\cdot}72$). For photography of the optogram, the spectral distribution and intensity are defined by the transmittances of the ocular media, the filters, and the optical components within the fundus camera. The retinal energy density during photography is calculated to be 7 Jm^{-2} when using setting no. 4 on the flash control unit and filters $F_2+HF_2+2E+0{\cdot}4$ ND. The ocular transmittance has been taken as 75 per cent for this calculation; details of this measurement and the calculation are given in the Appendix.

For the bleach, F_2 and the neutral-density filters are removed from the light path. The increase in the spectral bandwidth and transmittance results in an actinic retinal energy density which is expressed by $T_e \times 900$ Jm^{-2}, where T_e is the transmittance of the ocular media. Details of these calculations are also given in the Appendix. Taking a mean value of $T_e=60$ per cent over the spectral range 430–630 nm, the bleaching flash is estimated to provide an actinic retinal energy density of $5{\cdot}4\times10^2$ Jm^{-2}.

In previous studies on fundus densitometry, the retinal fluxes have been specified in photometric units. These may be related to the values given above by means of the following:

1 (scotopic) troland second $=1{\cdot}01\times10^{-4}$ Jm^{-2}, for $\lambda=505$ nm and a pupil diameter of 8 mm. Thus, while the value given above for photography compares well with the value of 4×10^4 troland s which was used by Highman and Weale (1973), the bleaching flash currently used is about three times less intense than their figure of $1{\cdot}82\times10^7$ troland s. The relationship between the fraction of pigment bleached and the retinal illuminance (Fig. 3, Ripps and Weale, 1969) indicates that the present flash will bleach about 55 per cent of the pigment. Thus, if the maximum optical density

difference that can be achieved in the eyes of normal subjects is taken to be 0·16–0·18 D, we may expect to measure a density difference of 0·09–0·10 D in these subjects with the present equipment.

The alignment and focus adjustment of the camera were carried out by using the red filter F_1 in the path of the white light from the bulb B_1. On setting 2 of the Zeiss power supply the retinal illumination was calculated to be 350 troland. The luminance of the image of the source formed in the pupil of the model eye was measured by means of a photometer*. The luminances of the additional LED fixation targets were adjusted by varying their input power so that they appeared to have the same luminosity as the surrounding field. The power spectrum of these LEDs is negligible at wavelengths shorter than 630 nm and their emission is confined to a narrow band in the deep red part of the spectrum.

Procedure

The patient is seated at the fundus camera in a darkened examination room. The pupil must have been fully dilated and dark adaptation allowed to proceed for at least 15 min before this. The plane of the film and the apertures are adjusted rapidly so as to be in focus with the retina. Since it is difficult for the operator to see much retinal detail in the dim red light, it is helpful to begin the adjustments while viewing the region around the optic disc which has a larger reflectance and is rich in structure. Note that a slight re-adjustment will be necessary to view different parts of the fundus but no correction for chromatic aberration is required. The required retinal area is then brought into the centre of the field of view with the moveable internal fixation target or one of the LED targets and the focus checked. A retinal area in which there are relatively few blood vessels should be selected as far as possible, so that the traces recorded by the scanning densitometer are smooth and thus easier to analyse. The aperture A_2 is brought into the optical path by pulling the shaft S_2, the xenon flash is activated by means of the switch Sw, and the shaft is pushed back; this completes the bleaching step. If the eye is still correctly placed, the filter F_2 is pushed into the light path, the retina is photographed, and F_2 is pulled back to its resting position. The camera shutter is set nominally to 1/25 s. The film is then advanced by one frame so that the camera is ready for another photograph or the next sequence. A readily available sensitive film† is used for this reading. The film is processed in complete darkness and according to the manufacturer's instructions.

Careful alignment of the patient's eye to the apparatus is particularly important in this technique, because it is essential to transmit all of the available flux into the patient's eye for bleaching. During photography, the spurious reflections and scatter from the eye that can so easily mask the image of the optogram, must be avoided. Note that with the subject's fixation on the periphery of the apertures A_1 or A_2, the pupil will appear to be elliptical as viewed along the optical axis of the apparatus. Thus there is a reduced margin for the transverse alignment of the image of the light source, formed in the subject's pupil. A misalignment would mean that a part of the beam would be occluded and this could cause a serious reduction in the retinal illumination. For a given patient, the focus and the fixation target require little, if any, adjustments on recalling the patient after a period of rest or further dark-adaptation. In order to ensure accurate fixation during the course of this procedure, the fixation target should be presented to the same eye as that used for recording the optogram.

Results and the analysis of the optogram

A positive print of a typical retinal photograph taken with this modified fundus camera is shown in Fig. 2. This was recorded from a subject in whom dark-adaptation and vision were normal. The rectangular optogram can be clearly seen in the centre of this photograph as an area of lower optical density. This area is crossed by the regularly spaced stripes caused by superimposition of the density graticule. It is important to note that the optical densities are reversed during the process of this photographic printing—that is, the bleached area in reality reflects more bluish-green light than the surrounding unbleached region so that it is more dense on the photonegative. The aperture A_2 used for bleaching was centred about 15° temporal to the fovea, along the horizontal meridian. The backs of the two LED fixation targets which

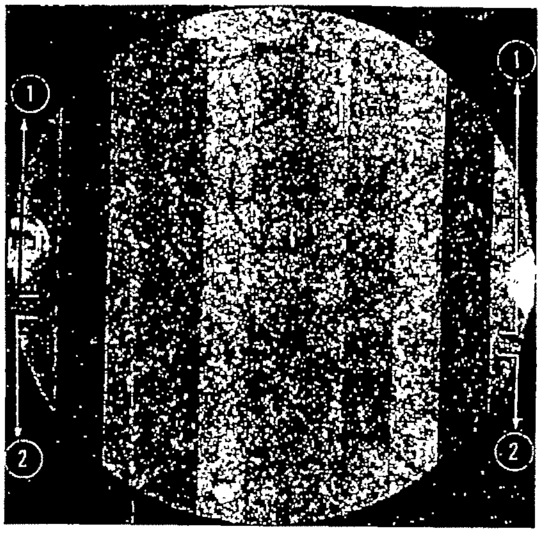

FIG. 2 *A positive photographic print of typical optogram recorded from normal fundus. Subject's point of fixation is marked by* LED *target at left edge*

are provided within the lens housing can also be seen; the subject's fixation is marked by the illuminated LED target at the left of the photograph.

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*Model 40A, made by UDT Inc, California, USA

†Kodak 2475

In order to obtain quantitative results from the fundus photograph, the photonegative has to be scanned in a microdensitometer; a double-beam recording microdensitometer* was used for the present work. The displacement of the trace-recorder, due to a change in the optical transmittance of the scanned sample, has to be initially calibrated; this was done by introducing known values of neutral-density filters in the path of the measurement beam. Then, using common experimental conditions for both measurements—for example, the same spot size and scan rate—the density-graticule and the photonegative are scanned in turn. The difference between the scans taken through the bleached area and the adjacent unbleached area is proportional to the true optical density difference. The proportionality constant is the transfer characteristic of the particular part of the film (Arnold and others, 1971). For a given region of the film if the step change due to the superimposed density graticule is the same for both scans, then this constant is unity. Thus deviations from unity can be noted and the results scaled accordingly. The procedure can best be illustrated by referring to Fig. 3 which shows the traces (corresponding to the scans taken through the sections indicated in Fig. 2). The traces are drawn about a datum line which is taken to be the base or fog level of the film. A scan of the particular density graticule which was used for this photograph is also shown in Fig. 3. Note, however, that this third trace has been drawn inverted so as to illustrate the point that the exposure received by the film which lies under the calibration strips is reduced. This local reduction of exposure can also be seen in the other two traces which are pulled down towards the datum in the regions containing the calibration strips. The calibration for the graticule is indicated in the centre of this figure. The transfer characteristic of this photonegative can be seen to be slightly above unity. The density contrast of the optogram formed in central part of this photograph—that is, 15–20° temporal—is about 0·1 D. The density difference can be determined more easily, in practice, when all three traces are available on separate sheets of transparent graph paper. The sheets containing the scans taken outside and through the bleached region are then viewed against the sheet for the graticule. The graticule is once again held inverted and used as a template.

These traces illustrate several additional interesting features. The traces are noisy and the reflectance varies across the retina. This variation is due to a variety of reasons, partly in the instrument and partly in the subject's eye—for example, the presence of blood vessels in the path of the scan or a non-uniform retinal reflex. Note, however, that the scale of this variation is either much smaller or else much larger than that due to the modulation impressed by the graticule on the fundus photograph. Thus it is easy to discriminate between the true density changes and the artefacts. The traces also illustrate the variation of the density difference across the retina. This variation is practically zero for the part of the retina nearer than 10° temporal to the fovea. It rises rapidly beyond this to a broad maximum in the region 15–30° temporal, in general agreement with the distribution of rods in the retina. For routine clinical investigations, one would be interested chiefly in the central portion of the photograph. Thus, as indicated above, a graticule is made so that it provides a density step of a value which is of the order of the density difference that one expects to measure from normal subjects. A marked reduction in the density difference recorded in a patient's eye would thus be readily seen to be much smaller than this step. The two outermost strips are well outside the expected range. However, they illustrate the fact that even when the illumination on the film is reduced by 0·35 density units, an appreciable density difference can still be recorded. This difference can of course be achieved only from optograms formed in regions

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*Model 3c, made by Joyce-Loebl Ltd

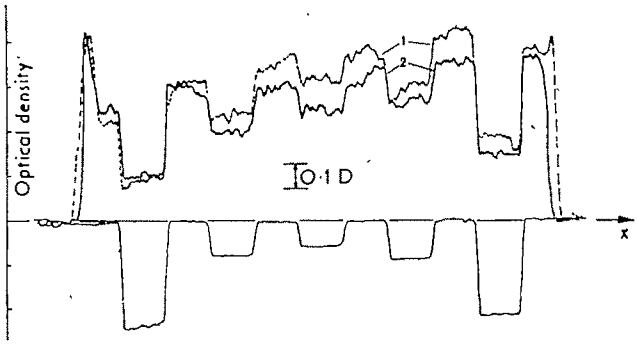

FIG. 3 *Trace recordings produced by scanning microdensitometer. Traces 1 and 2 are due to scans taken through corresponding sections which are indicated in Fig. 2. Lowest trace is scan of particular density graticule used to superimpose calibration. Scan has been drawn inverted so as to indicate that exposure of film underlying density strips is reduced. Ordinate represents optical density; abscissa represents distance along horizontal meridian on fundus*

of the retina distal from the macula. Thus the film as such appears to have an operational range which encompasses the gross variations of retinal reflex across the retina. Note also that in this graticule the densities of the steps increase away from the vertical midline. Thus a graticule such as this may be used to photograph the optogram in corresponding regions of either eye without requiring the replacement of graticules during measurements on both eyes.

Discussion

This example of the use of the modified fundus camera was typical; a clinical study of various retinal disorders using this apparatus is in progress and full results will be described in due course. Thus the comments below refer mainly to points of technique. In regular use, this modified fundus camera has proved to be no more difficult to use than is the normal camera for routine fundus photography. As the method provides a rapid, convenient means of supporting the measurements of associated retinal tests in diseases such as night-blindness, routine densitometric measurements may also be carried out in the same clinic with this apparatus.

The maximum flux available from the present equipment is insufficient to bleach all the visual pigment within a given region. The flux could be increased but only by modification, perhaps extensive, of the optics or the flash unit. However, as established by Highman and Weale (1973) in cases such as retinitis pigmentosa, the density differences in a given retinal region are much lower, and the visual thresholds of the same retinal region are much higher, than those in normal subjects. Therefore, for the assessment of such cases the apparatus may be used without any further modifications. It should be noted that simply increasing the incident flux may not give a markedly denser optogram, because short intense flashes of light can bleach only up to a limit of 70–80 per cent of the available pigment because of photoregeneration (Williams, 1974). Furthermore, the associated heating effect of the intense retinal illumination may well produce a deleterious effect—that is, oedema. The optical effect of this oedema is partially to counteract the density difference due to the bleach (Weale, 1968). Its magnitude, however, is said to be independent of the wavelength of light used for the measurement so that it may be quantified by measurements outside the absorption spectrum of the pigment. In order to ascertain whether oedema had been caused, a series of four or five fundus photographs were taken in deep-red light immediately after the retina had been bleached and at half-min intervals subsequently. The filter F_2 was replaced by a suitable deep-red colour filter*. In these photographs, no density difference corresponding to the bleaching aperture could be seen in the region of the optogram. The experimental conditions in the earlier fundus densitometric measurements were markedly different from those used currently—for example, Highman and Weale (1973) used a continuous 10 s intense exposure for bleaching—and therefore comparative assessments of the various procedures are difficult to make. In the previous studies, only the photometric effect of the bleaching light was specified, whereas in the present approach, both the actinic and the total retinal flux densities are estimated. Thus the total flux entering the eye can also be calculated (see Appendix).

This apparatus cannot be used in its present form at large viewing angles—that is, no larger than about 15° in either the vertical or the horizontal meridians. In order to do so, the image of the flash source which is formed in the subject's pupil would need to be reduced without reducing the incident flux. This reduction in the pupillary area as a function of the viewing angle was measured by Jay (1961). A smaller pupillary image would additionally reduce the variation in the retinal illumination due to the involuntary eye movements. These are particularly noticeable in older patients in whom more care is required for alignment. Note that a slight variation in the retinal illumination—for example, as a result of ocular absorption or small eye movements—does not restrict the use of this reflectometric method of measurement because a differential measurement is involved. The reduction in the retinal illumination during the bleaching step, however, could be significant since the density contrast of the optogram would be reduced. The reduction in the flux as a result of absorption—for example, in the lens—could be compensated by an appropriate increase in the incident flux using the data established by Said and Weale (1959), or by a specific measurement in a particular case.

Summary

A technique based on the method of differential fundus reflectometry is used to assess the availability of rhodopsin in the eye. A defined part of the dark adapted fundus is bleached by a short intense flash of light. The fundus is subsequently photographed in order to record the flux reflected from the bleached area, the optogram, and the surrounding unbleached region. This procedure requires only a few simple modifications to a Zeiss fundus camera before it can be used routinely in the clinic.

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*Ilford No. 608

The use of the Zeiss fundus camera for fundus densitometry was suggested by Professor R. A. Weale whose keen interest during the modifications and the clinical trials was invaluable. The modifications to the camera were carried out by Mr G. Mould.

Thanks are also due to Mr P. E. Cleary for collaboration with the clinical development.

Appendix

MEASUREMENT AND ASSESSMENT OF THE RETINAL FLUX

The absorbances A_λ of the various spectral filters used in the procedure and for calibration were measured in a dual-beam scanning spectrophotometer*. The results are tabulated below:

Filter	*Absorbance* (*density*)	A_λ (at $\lambda = 505$ nm)
F_2	0·60	(Half power bandwidth: 10 nm)
HF_2	0·07	
Wratten 2E	0·03	

The flux density in the retinal plane which was simulated within the model eye was measured by a fast-response photodiode†. The photodiode was operated in the photoconductive mode, using a bias of −45 V on its guardring electrode. The photocurrent was fed directly into an operational amplifier which was constructed from an integrated circuit, type LM 308. This was wired so as to perform either as a linear current-to-voltage converter or an integrator. Thus the envelope of a photocurrent pulse resulting from the detection of a xenon flash could be viewed on an oscilloscope or the integral of the current pulse could be measured by means of a voltmeter. The linearity of the operational-amplifier circuit was checked by injecting pulses of current from a pulse generator and through suitable known values of resistors. The response time (measured between the 10 per cent and 90 per cent amplitude points) was less than 20 µs, a value considerably less than the rise-time of the xenon flash. A capacitor of 10 µFarad was used in the feedback path of the operational amplifier in order to measure the total charge of one pulse of photocurrent. Using $F_2 + HF_2 + 2E + 1{\cdot}3ND$ filters within the light path of the fundus camera and setting no. 4 on the flash control unit, the output was $130 \pm 3{\cdot}7$ mV (mean of five flashes, ignoring the first flash). Thus the charge accumulated was $1{\cdot}3 \times 10^{-6}$ C per flash. The response sensitivity of the photodiode is 0·217 A/Watt, at $\lambda = 505$ nm, and the active area is $5{\cdot}1 \times 10^{-6}$ m^2. Thus the energy density received by the photodiode at the simulated retinal plane is 1·18 Jm^{-2}. Note that when the flash is first fired after a rest period of a few minutes, the flux from the first flash is about 5 per cent higher than that of the subsequent flashes which are fired at regular intervals of, say, 5 or 10 s.

During the retinal photography step, the filters $F_2 + HF_2 + 2E + 0{\cdot}4$ ND are used in the fundus camera. Taking the transmittance of the ocular media as 75 per cent at $\lambda = 505$ nm (Table 2·7, Wyszecki and Stiles, 1967) the retinal energy density is 7·04 Jm^{-2}. The retinal energy density may then be calculated for any given combination of filters inserted in the fundus camera, given the spectral distribution of the xenon flash-discharge source. Although there are several narrow peaks in the 460–490 nm band, in most applications the distribution may be taken to be essentially flat over the range 400–630 nm. Thus the use of a broad spectral band for bleaching, say, from 430–630 nm, increases the total flux by about 300 times more than that used during photography. If we take the mean transmittance of the ocular media as 70 per cent, the retinal energy density within this spectral band is about $1{\cdot}5 \times 10^3$ Jm^{-2}.

In order to calculate the increase in the actinic flux during the bleaching step, the absorption spectrum of rhodopsin was used (Crescitelli and Dartnall, 1953). In the spectral range 430–630 nm, the increase is 9·6 times more than that in a 10 nm bandwidth centred at 505 nm. Thus, the removal of the neutral density filter and F_2 from the light path will increase the actinic flux at the retinal plane to: $1{\cdot}18 \times 9{\cdot}6 \times \log_{10}^{-1}(1{\cdot}9) \times T_e$ or $900 \times T_e$ Jm^{-2}.

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*Perkin Elmer, model 402

†SGD 100A, a silicon PIN type, supplied calibrated by E. G. and G. Inc, Boston, USA

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Plasma amino-acids in hereditary retinal disease
Ornithine, lysine, and taurine

ELIOT L. BERSON, SUSAN Y. SCHMIDT, AND ARNOLD R. RABIN
From the Berman-Gund Laboratory for the Study of Retinal Degenerations, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston

In one previous report plasma free amino-acids were found to be normal in seven patients with hereditary retinitis pigmentosa (Campbell and Tonks, 1962); however, the genetic types studied and the amino-acids measured were not specified. In more recent investigations, a reduction of plasma taurine and an increase in plasma ornithine have been demonstrated in association with retinal degenerations. A severe and selective plasma taurine deficiency was accompanied by the development of photoreceptor cell degeneration in cats which were given a taurine-free casein diet (Berson, Hayes, Rabin, Schmidt, and Watson, 1976; Hayes, Carey, and Schmidt, 1975; Hayes, Rabin, and Berson, 1975; Rabin, Hayes, and Berson, 1973; Schmidt, Berson, and Hayes, 1976). Delays in the cone electroretinogram (ERG) similar to those seen in patients with early stages of hereditary retinitis pigmentosa (Berson, Gouras, and Hoff, 1969; Berson and Howard, 1971; Berson, 1974) were detected in these taurine-depleted cats. Nondetectable ERGs with plasma ornithine levels 10 to 20 times higher than normal have been reported in patients with recessively inherited gyrate atrophy of the choroid (Simell and Takki, 1973; Takki, 1974a, b; Takki and Simell, 1974).

The present study was undertaken in order to determine plasma ornithine and taurine concentrations in patients who had different genetic types of retinitis pigmentosa and allied chorio-retinal degenerations. Precursors and metabolites of ornithine and taurine as well as levels of lysine (an analogue of ornithine) were also measured.

Methods

Plasma free amino-acids were measured in 41 patients with representative types of hereditary retinal degenerations, six relatives of patients with gyrate atrophy of the choroid, and 13 normal subjects. Patients included those with retinitis pigmentosa (dominant, four; sex-linked, three; autosomal recessive, 15; Usher's syndrome, two; and Laurence-Moon-Biedl (LMB) syndrome, two); juvenile macular degeneration, four; choroideremia, three; generalized choroidal sclerosis, three; and gyrate atrophy of the choroid, five. Among the patients with autosomal recessive retinitis pigmentosa, six had signs of early macular degeneration with visual acuity of less than 20/50. Two patients with juvenile macular degeneration had Stargardt's disease, and two had fundus flavimaculatus.

Patients with gyrate atrophy (Patients 1–5) and their relatives (Patients 6–11) were from four families. Patients 3 (parents 8 and 9) and 4 (sibling 10) were of Portuguese extraction; Patients 1 and 2 (parents 6 and 7) were of Swedish extraction; and Patient 5 (parent 11) was of English extraction. Parents of Patient 3 were first cousins. All patients had myopia. Refractive errors ranged from −1·00 dioptre (Patient 1) to −16·00 dioptres (Patient 2). Ophthalmoscopical examination was performed on all patients and their relatives. Full-field ERG testing was done on the patients using techniques described previously (Berson and others, 1969). For comparison, fundus examination and ERG were carried out on one child (Patient 12), aged 11 years, previously described (Shih, Efron, and Moser, 1969) and known to have hyperammonaemia, hyperornithinaemia, and homocitrullinuria. In addition to plasma amino-acids, levels of blood ammonia (NH_3) and blood urea nitrogen (BUN) were measured in four of the five patients with gyrate atrophy and in five of the six relatives.

The amino-acid analyses were performed as described previously (Stein and Moore, 1954) using a Durrum 500 automatic amino-acid analyzer. Fasting blood samples were collected and centrifuged, and the plasma was immediately deproteinized with 30 mg/ml sulphosalicylic acid (Perry and Hansen, 1969). The deproteinized supernatents were stored at a temperature of −70°C.

Before amino-acid analysis, the pH of each extract was adjusted to pH 2·2 with lithium hydroxide crystals, and an aliquot of 40 µl was applied to the ion exchange chromatography column (Durrum DC-4A resin). The samples were eluted from the column by a continuous lithium buffer gradient (from 0·24 M, pH 2·89 to 1·19 M, pH 6·5) at a rate of 6·3 ml/h and at three temperatures (41°C, 45°C, and 65°C). The results obtained using this method were reproducible within a ±8 per cent range.

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Requests for reprints: Dr E. L. Berson, Berman-Gund Laboratory, 243 Charles Street, Boston, Massachusetts 02114, USA

Table I *Plasma amino-acids (nmol/ml) in normal subjects, patients with retinal degenerations, and relatives of patients with gyrate atrophy*

		Retinitis pigmentosa									
	Normal	*Dominant*	*Sex-linked*	*Autosomal recessive*	*Usher's syndrome*	*LMB syndrome*	*Juvenile macular degeneration*	*Choroideremia*	*General choroidal sclerosis*	*Gyrate atrophy*	*Gyrate atrophy relatives*
No. of subjects	13	4	3	15	2	2	4	3	3	5	6
Age range (years)	9–58	10–28	14–28	11–52	11–31	6–17	11–25	30–33	17–39	7–18	13–44
Taurine	57 ±28	40 ±8	40 ±0	44 ±8	60	50	45 ±13	50 ±17	57 ±12	46 ±9	45 ±5
Aspartic acid	12 ±4	10 ±0	13 ±6	12 ±4	—	—	—	10 ±0	10 ±0	10 ±0	8 ±4
Glutamine	863 ±232	733 ±99	723 ±331	983 ±170	950	—	640 ±113	955 ±245	965 ±295	706 ±308	717 ±191
Serine	119 ±17	118 ±10	117 ±6	123 ±30	100	70	110 ±18	103 ±21	113 ±46	126 ±15	93 ±21
Glutamic acid	32 ±13	28 ±5	27 ±6	39 ±18	35	30	—	43 ±23	33 ±15	24 ±9	32 ±10
Proline	181 ±66	138 ±69	207 ±74	201 ±90	130	110	128 ±17	193 ±58	170 ±92	224 ±77	270 ±117
Citrulline	32 ±8	33 ±6	30 ±10	29 ±12	15	10	48 ±13	30 ±10	27 ±6	26 ±5	270 ±5
Cysteine	120 ±22	116 ±10	126 ±12	124 ±22	90	90	80 ±34	120 ±20	100 ±20	100 ±20	90 ±10
Methionine	28 ±9	28 ±5	33 ±12	29 ±5	30	20	28 ±5	20 ±0	23 ±6	22 ±4	25 ±8
Ornithine	61 ±16	65 ±10	63 ±31	65 ±12	80	60	45 ±10	73 ±15	57 ±15	*1,026 ±277	‡102 ±29
Lysine	167 ±19	158 ±5	160 ±40	175 ±47	200	130	155 ±13	193 ±40	167 ±21	†102 ±37	158 ±19
Arginine	103 ±24	95 ±24	103 ±15	101 ±28	75	70	85 ±24	107 ±46	77 ±12	88 ±8	80 ±13

The values represent the mean ± SD

Significantly different from normal *P < 0·0005, †P < 0·0025, ‡P < 0·005

Results

Table I shows that in five patients with gyrate atrophy of the choroid the mean plasma ornithine is 17 times higher than in normal subjects (Student's two-tailed *t* test, P < 0·0005). The mean plasma ornithine value for relatives of patients with gyrate atrophy is 1·7 times higher than normal (P < 0·005). Mean plasma lysine of the patients with gyrate atrophy is lower than normal (P < 0·0025) while that of the relatives of patients with gyrate atrophy is normal. All other plasma amino-acids measured in patients with gyrate atrophy, relatives of patients with gyrate atrophy, and patients with other representative types of hereditary chorio-retinal degenerations are within normal limits.

Table II shows plasma ornithine and lysine values for each patient with gyrate atrophy. The minimum increase is 10 times above normal, and the maximum is 22 times. Four out of five patients have lower-than-normal plasma lysine. Four out of six relatives have plasma ornithine levels outside the normal range, and all have normal lysine values. Blood NH_3 and blood urea nitrogen levels are normal in all patients.

Ophthalmoscopical examination showed typical changes in gyrate atrophy in Patients 1–5. Atrophy appeared most extensive in the midperipheral fundus of Patients 2 and 3 and could also be seen in the posterior pole. Atrophy was visible only in the midperiphery in Patients 1 and 4. ERGs were nondetectable in Patients 2–5 and were 75 per cent below normal in amplitude in Patient 1. Relatives had no visible fundus abnormalities.

Patient 12 who was known to have hyperornithinaemia, hyperammonaemia, and homocitrullinuria (Shih and others, 1969) had a tenfold increase in plasma ornithine (650 nmol/ml) at a time when the fundus examination and ERG were normal.

Table II *Biochemical findings in patients with gyrate atrophy and their relatives*

		Age	*Sex*	*Plasma ornithine nmol/ml*	*Plasma lysine nmol/ml*	*Blood NH_3 µg per cent*	*BUN mg per cent*
Patients	1	7	Female	1170	110	86	17
	2	8	Female	880	60	110	16
	3	18	Female	1140	90	57	16
	4	11	Male	620	160	82	20
	5	17	Male	1320	90	—	—
Relatives	6	31	Male	150	170	77	13
	7	30	Female	70	130	84	16
	8	44	Male	110	180	60	10
	9	40	Female	90	140	60	11
	10	13	Female	110	170	55	17
	11	50	Male	80	160	—	—
Normal range				40–80	130–210	< 110	10–20

Discussion

This investigation has confirmed previous reports (Simell and Takki, 1973; Takki, 1974a, b; Takki and Simell, 1974) that the level of plasma ornithine was much higher than normal in patients with gyrate atrophy of the choroid. Other hereditary degenerations involving the choroid and retina, in particular choroideremia and generalized choroidal sclerosis, were not associated with abnormal levels of plasma ornithine. In addition, the level of lysine, an analogue of ornithine, was lower than normal in four of five patients with gyrate atrophy of the choroid, and the mean value was significantly different from normal ($P < 0{\cdot}0025$). Takki (Takki, 1974a) also showed that the range of lysine values was low in comparison with the normal range in the plasma and aqueous humour of her patients, but no statistical analysis was given.

High plasma ornithine levels alone may not necessarily lead to the development of gyrate atrophy of the choroid. A threefold increase in plasma ornithine was reported in two siblings with mental retardation and normal fundi (Bickel, Feist, Müller, and Quadbeck, 1969). Patient 12 in this study with hyperornithinaemia, hyperammonaemia, and homocitrullinuria (Shih and others, 1969), had had a tenfold increase of plasma ornithine for at least nine years but was found to have a normal fundus appearance and a normal ERG. The plasma ornithine of Patient 12 was comparable with that observed in Patient 4 who was of the same age with fundus changes of gyrate atrophy and a nondetectable ERG.

It is unlikely that the high plasma ornithine in gyrate atrophy has resulted from an enzyme deficiency in the Krebs-Henseleit urea cycle (see Fig. 1). Patients with a deficiency of ornithine transcarbamylase (OTC) have shown high levels of blood ammonia NH_3 and normal plasma ornithine (Efron, 1967; Levin, Abraham, Oberholzer, and Burgess, 1969). Other known enzyme defects in the cycle have usually been associated with high levels of blood ammonia (NH_3) and an increase of one or more amino-acids in the cycle (Efron, 1967; Shih and Efron, 1972). In contrast, patients with gyrate atrophy have the unusual combination of normal levels of NH_3 and high levels of ornithine as well as normal citrulline and arginine. Therefore, the high level of ornithine is probably due to some abnormality not involving the urea cycle. Possible explanations include decreased activity of ornithine ketoacid transaminase (OKT) or ornithine decarboxylase.

A reduction of 70 to 80 per cent in the activity of OKT has been observed in two siblings with normal levels of blood NH_3 and a threefold increase in plasma ornithine (Bickel and others, 1969). This raises the question of whether an OKT deficiency alone could account for an increase of 10 to 20 times of ornithine in patients with gyrate atrophy. In one patient with gyrate atrophy, liver biopsy showed an OKT deficiency, but this finding awaits confirmation (Takki, personal communication). Shih found normal OKT activity (Shih and Schulman, 1970) and a 70 per cent reduction in ornithine decarboxylase activity (Shih and Mandel, 1974) in her patient (Patient 12) with a tenfold increase of plasma ornithine. Decarboxylase activity has not been measured in gyrate atrophy. If a decarboxylase had higher affinity for lysine than for ornithine, this could explain the high mean plasma ornithine and the low mean plasma lysine in patients with

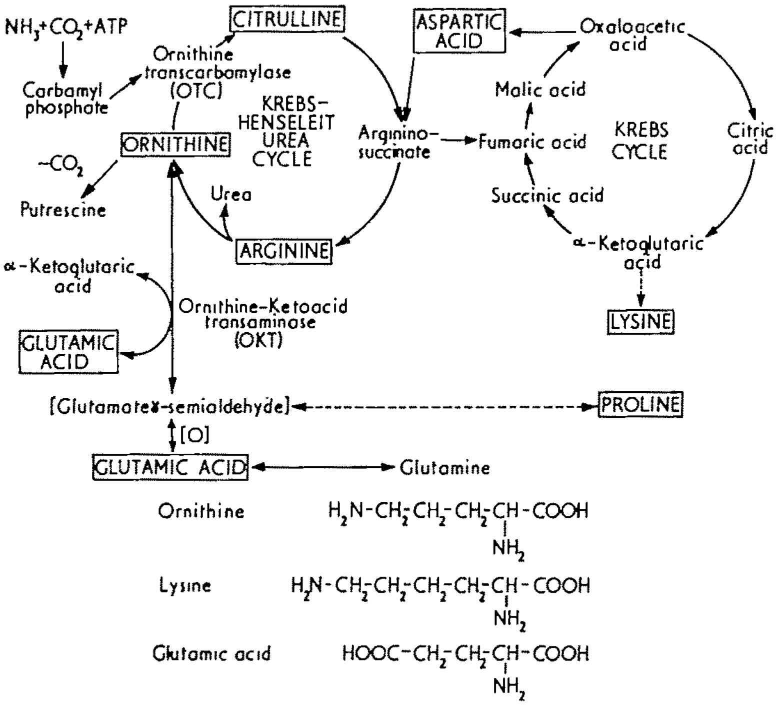

FIG. 1 *Ornithone metabolism: known pathways of ornithine metabolism are illustrated. Amino-acids (capitalized) were measured in plasma of patients with hereditary chorio-retinal degenerations, relatives of patients with gyrate atrophy and normal subjects (Efron,* 1967; *Schepartz,* 1973; *Shih and Efron,* 1972; *White and others,* 1968)

gyrate atrophy, and this could also result in altered ratios of polyamine metabolites of ornithine and lysine (putrescine and cadaverine, respectively) in the plasma and in the retina. The role, if any, of ornithine and lysine as well as their polyamine metabolites in retinal function is not known.

Several free amino-acids have been found in the normal retinae of many species. These include not only ornithine and lysine but also taurine, glutamine, glutamic acid, glycine, alanine, γ-aminobutyric acid, aspartic acid, and histidine (Pasantes-Morales, Klethi, Ledig, and Mandel, 1972). Evidence suggests that glycine (Ehinger and Lindberg, 1974) and γ-aminobutyric acid (Graham, 1974) are neurotransmitters in the retina, but the role of the other free amino-acids is not known. Taurine and ornithine have not been shown to be incorporated into proteins (White, Handler, and Smith, 1968). Taurine, present in the normal human retina (Kubiček and Dolének, 1958), exceeds by threefold the level of any other free amino-acid in the retinae of many species (Berson and others, 1976; Cohen, McDaniel, and Orr, 1973; Hayes and others, 1975a; Kennedy and Voaden, 1974; Macaione, Ruggeri, De Luca, and Tucci, 1974; Pasantes-Morales and others, 1972; Schmidt and others, 1976).

Recent studies in the cat have shown that taurine has a biological role in maintaining photoreceptor cell viability. All cats fed a taurine-free casein diet developed a selective decrease in plasma and retinal taurine concentrations within 10 weeks and evidence of retinal degeneration was visible with the ophthalmoscope by 23 weeks in the area centralis. Initially the area centralis (comparable to the macula in man) appeared to be most affected, but taurine was similarly reduced in the central and peripheral retina, and by 1 year, cats had degeneration of most photoreceptor cells. The cat, as well as man, has a low level of liver decarboxylase activity (Jacobsen and Smith, 1968) such that conversion of cysteic acid or cysteine sulphinic acid (see Fig. 2) to taurine proceeds at a slow rate. In the cat, supplementation of the casein diet with taurine precursors (methionine and cysteine) did not prevent the development of either taurine deficiency or the retinal degeneration (Berson and others, 1976). Delayed cone b-waves in the ERGs recorded from the taurine-deficient cat were similar to those recorded from patients with early stages of retinitis pigmentosa. The present investigation shows that taurine and its precursors (Fig. 2) were normal in the plasma of patients with different genetic types of retinitis pigmentosa and patients with hereditary juvenile macular degeneration. However, a local defect in taurine uptake or metabolism in the photoreceptor cells of these patients has not been excluded.

The associations of raised levels of plasma ornithine and low plasma lysine with gyrate atrophy of

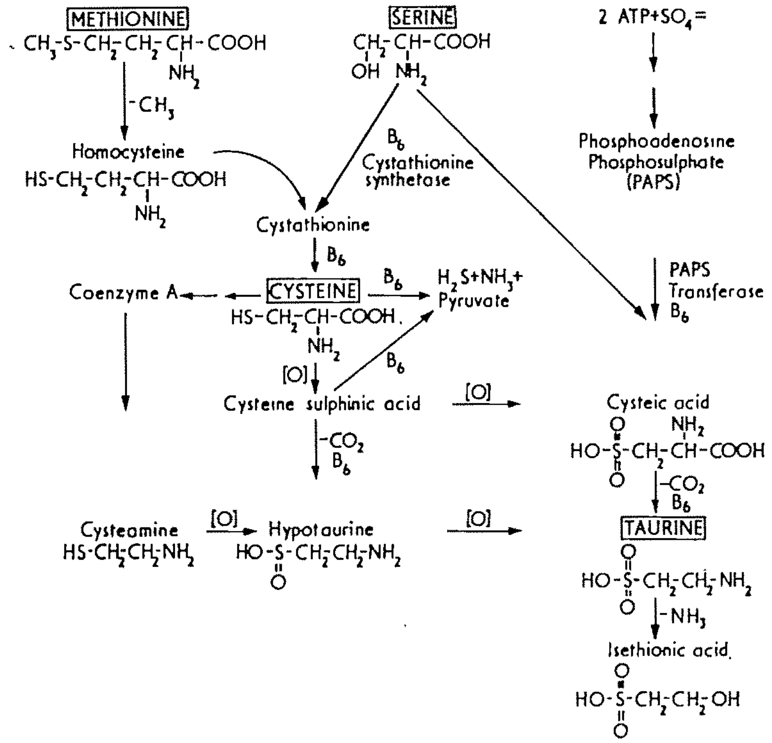

FIG. 2 *Taurine metabolism: known pathways of taurine metabolism are illustrated. Amino-acids (capitalized) were measured in plasma of patients with hereditary chorio-retinal degenerations, relatives of patients with gyrate atrophy and normal subjects (Efron,* 1967; *Jacobsen and Smith,* 1968; *Martin, Truex, Tarka, Hill, and Gorby,* 1974; *Roy and Trudinger,* 1970)

the choroid in man, and low plasma and retinal taurine with retinal degeneration in the cat, have suggested new areas for research into the pathogenesis of retinal degenerative diseases. Further studies are needed to quantitate the free amino-acids in the human retina and to study the metabolism of these amino-acids in normal animals and in animals with retinal degenerations.

Summary

Plasma free amino-acids were measured in 41 patients with hereditary chorio-retinal degenerations including 26 with retinitis pigmentosa and five with gyrate atrophy of the choroid, six relatives of patients with gyrate atrophy, and 13 normal subjects. Patients with gyrate atrophy had very increased levels of ornithine and slightly decreased mean lysine values. Most relatives had slightly increased ornithine. Taurine, known to be deficient in the plasma of casein-fed cats with photoreceptor degeneration, was normal in all patients. Amino-acid precursors and metabolites of ornithine and taurine were also normal in the plasma. Although the association of high ornithine and gyrate atrophy appears constant, high levels of ornithine alone do not necessarily lead to this degeneration; one patient with known hyperammonaemia, homocitrullinuria and a tenfold increase in plasma ornithine was found to have a normal fundus appearance and normal electroretinogram.

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Retinal vein occlusion: long-term prospects
10 years' follow-up of 143 patients

K. RUBINSTEIN AND E. B. JONES
From the Medical Ophthalmology Clinic, Birmingham and Midland Eye Hospital

Between the years 1960 and 1965, 226 patients were referred to the Medical Ophthalmology Clinic of the Birmingham and Midland Eye Hospital with the diagnosis of retinal vein occlusion. The first 120 consecutive patients were reported upon in 1964 in a paper on the pathogenesis of the condition (Paton, Rubinstein, and Smith, 1964). It was then decided to review the patients in 10 years' time in order to assess their long-term prospects regarding life expectancy, further morbidity, late ocular changes, and visual prognosis.

Clinical material

Of the 226 patients, 35 who were seen mainly in the final year of recruitment were excluded from our present study because of incomplete initial documentation, and 45 could not be traced: 18 moved away, 10 left the city because of redevelopment and demolition of their homes, 17 stopped responding to our letters, and two were retrospectively re-diagnosed as cases of retinal vasculitis. Of the remaining 143 patients, 93 were found alive and were re-examined, 50 had died and we were able to establish the cause of death in 29 of them. Of the 143 patients under review, 75 were men (52·5 per cent) and 68 women (47·5 per cent). Of the survivors, 47 were men and 46 were women. Of those who died 28 were men and 22 were women.

The mean age at the time of first visit was 56 years for men and 63 for women (Fig. 1). Raitta (1965) found that men tended to be affected one decade earlier than women, and while from our material this appeared to be so for the sixth decade, it was not otherwise a striking feature.

Altogether 73 right eyes were affected and 84 left eyes, an approximately equal distribution; both eyes were affected in 14 cases. The central retinal vein was affected in 80 eyes (five bilaterally), and a branch occlusion was seen in 77 eyes (six bilaterally). The number of eyes affected by central retinal vein occlusion was about equal to those affected by branch occlusion, similar to the findings of Foster Moore (1924) and Raitta (1965). The respective figures are 55 eyes with central and 48 eyes with branch occlusion for 93 survivors, and 25 eyes with central and 29 eyes with branch occlusion for the 50 who died.

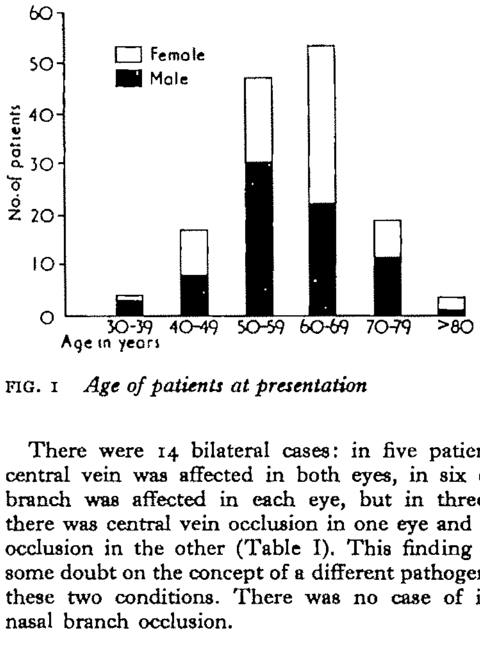

FIG. 1 *Age of patients at presentation*

There were 14 bilateral cases: in five patients the central vein was affected in both eyes, in six cases a branch was affected in each eye, but in three cases there was central vein occlusion in one eye and branch occlusion in the other (Table I). This finding throws some doubt on the concept of a different pathogenesis of these two conditions. There was no case of isolated nasal branch occlusion.

CLINICAL PICTURE

All the patients presented with various grades of classical 'retinitis haemorrhagica', with haemorrhages, exudates, venous engorgement, and optic disc swelling. Arteriolar involvement and vitreous haemorrhages were more frequent in the patients who died than in those who survived, and this may be of prognostic interest (Table II).

FOLLOW-UP

The mean duration of follow-up for the series was 9·8 years for the surviving group and 5·4 years for those

Table I *Bilateral involvement (14 patients)*

Central vein	—central vein	5
Central vein	—superior temporal vein	2
Central vein	—inferior temporal vein	1
Superior temporal	—superior temporal vein	4
Superior temporal	—inferior temporal vein	2

Address for reprints: K. Rubinstein, FRCS, Birmingham and Midland Eye Hospital, Church Street, Birmingham B3 2NS

Table II *Initial fundus (special features)*

Survivors (93)		*Percentage*	*Dead* (50)	*Percentage*
Arteriolar involvement	1	1·1	4	8
Vitreous haemorrhage	2	2·2	4	8

who died (range 2 weeks to 13 years) (Fig. 2). Of those patients who survived, 19 had their final assessment during 1971–73. The remainder were examined in 1974.

MORBIDITY

Of the 93 patients reviewed, 83 had no significant complaints about their general health during the follow-up. Seven patients had had non-fatal cerebrovascular episodes and three had myocardial ischaemia. Only three (2·1 per cent) of the total series of 143 patients were affected by diabetes; one of them had suffered from the disease for many years before the vein occlusion.

It has been stated (Gubner, 1962) that 20 per cent of the adult population is hypertensive (that is, the diastolic pressure is 100 mm Hg and over). Of the 50 patients who were now dead, 34 (68 per cent) were hypertensive on presentation, 19 (38 per cent) having diastolic pressures of more than 120 mm Hg. Even of the 93 patients who survived, 60 (64 per cent) were hypertensive, 17 (18 per cent) having a diastolic pressure of more than 120 mm Hg (Fig. 3).

MORTALITY

Just under half of the patients surveyed were found to have died (50); this mortality would be expected in the age group concerned (Registrar General's Statistics for England and Wales); but the causes of death are markedly different. Among 29 cases in which the cause of death was established, 23 (79·4 per cent) patients died of vascular disease and only six (20·6 per cent) of malignancy. This number of deaths from vascular disease—cerebral or cardiac—is about double the national figure and the number of deaths from malignant disease is proportionally lower (Table III).

OCULAR CHANGES

The final ophthalmoscopic fundus examination showed a variety of pathological changes, only 11 eyes showing regression to normal (fluorescein angiography was not performed at the final review) (Table IV). The striking finding was the high number of eyes affected by optic atrophy (39·8 per cent) and neovascularization of the optic disc (33·3 per cent) alone or accompanied by other fundus abnormalities. There was a high incidence of macular degeneration which could, however, be expected. Significantly, 15 unilaterally affected patients showed a well-established hypertensive retinopathy in the fellow eye.

Seven patients suffered from primary glaucoma: five were under treatment at the time of vein occlusion and two were diagnosed at the final re-examination having already developed glaucomatous cupping of the disc

Years	2/52	6/12	1	2	3	4	5	6	7	8	9	10	11	12	13
Alive 93 patients								1	4	14	17	29	17	7	4
Dead 50 patients	1	1	4	6	4	3	7	4	4	6	7	3			

Mean follow-up time=9·8 years (live group)

FIG. 2 *Duration of follow-up*

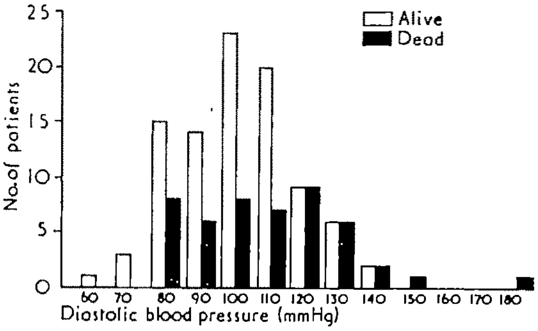

FIG. 3 *Initial blood pressure*

Table III *Cause of death in 29 patients documented*

Cause	*Men*	*Women*	*Total*
Myocardial infarction	8	4	12
Cerebrovascular accident	3	5	8
Generalized arteriosclerosis	1	1	2
Renal disease	0	1	1
Malignant disease	2	4	6

Table IV *Final fundus—abnormal findings (single or combined)*

Normal	11
Optic disc atrophy	37
Optic disc neovascularization	31
Retinal neovascularization	21
Vascular involution	8
Retinal haemorrhage	8
Macular degeneration	33
Circinate retinopathy	2
Vitreous haemorrhage	11
Retinal detachment	1
Glaucoma (primary binocular)	7
Glaucoma (secondary uniocular)	4
Diabetic retinopathy	3
Excision of eye	1

in both eyes. This contrasts oddly with two recent series: a 35 per cent incidence of glaucoma was reported by Raitta (1965) and 20 per cent was estimated by Reed and Drance (1972). There were also only four cases of thrombotic glaucoma, one eye requiring excision, an incidence of 4·3 per cent as compared with 12 per cent reported by Vannas (1961), 10–30 per cent as reported by Becker and Schaffer (1961) and 20 per cent as reported by Raitta (1965).

VISUAL ACUITY

The pattern of final visual acuity shows a significant dip in the moderate range 6/18–6/36; only 23 eyes (22·5 per cent) were in this range. Twice as many eyes, 42 (41·2 per cent) had 6/12 or better vision, and nearly twice as many eyes, 37 (36·3 per cent) had 6/60 vision or worse (Fig. 4).

Such an 'all or nothing' response can be found as a result of random severe insult to the eye—for example, as a consequence of injury by intraocular foreign body (Rubinstein, 1954). We found no difference in visual prognosis for the central as opposed to branch vein occlusions.

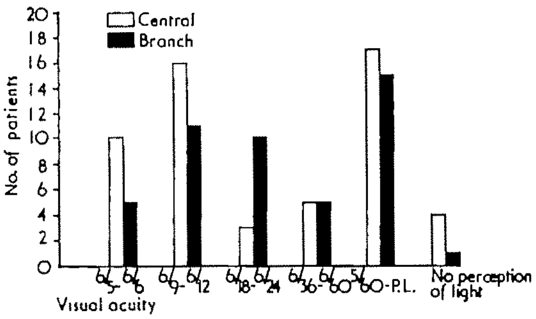

FIG. 4 *Final visual acuity*

Conclusions

Our comments regarding the specific questions posed at the beginning of this review are as follows:

1. The life expectancy of patients with retinal venous occlusion is not shortened (when compared with statistics relating to similar age groups of population in the United Kingdom). When they die, however, the proportion of vascular cause of death—cardiac and cerebral—is about double.
2. The morbidity of patients affected by retinal venous occlusion is low, normal for their age group. It is worth noting that only three patients were diabetics. Hypertension is a crucial problem, and considered relevant to the condition.
3. The fundus shows finally, gross permanent changes in a high percentage of eyes; optic disc atrophy was found in two-fifths of patients, optic disc vascularization in one-third, and macular degeneration in one-third.
4. The visual prognosis is unpredictable. It mainly depends on the degree of the involvement of the macula and on the length of time that the macula is in a state of oedema. Two-fifths of the patients retained good visual acuity, but two-fifths fared very badly.

We should like to acknowledge the help given to us during the investigation by Miss Sandra Smith. Dr M. Merz of Warsaw conducted the 1973 part of the review.

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Retinoblastoma occurring in four successive generations

CLIVE MIGDAL*
From the Department of Ophthalmology, St Bartholomew's Hospital, London

The hereditary aspect of retinoblastoma, the most common intraocular tumour in childhood, has been well established (François and van Leuven, 1964; Vogel, 1967; Sorsby, 1972; Warburg, 1974).

These tumours have been reported in up to three successive generations (Morgan and Bair, 1968), but there is no proven evidence of retinoblastoma occurring in four successive generations.

This report deals with a family in which retinoblastoma has been found in four generations, and it also emphasizes that an apparently unaffected individual can still transmit the affected gene to his offspring, who may, in turn, manifest the disease.

Case reports

CASE 1

(I/8, male, born 1891, the youngest of a large family, having five older brothers and two older sisters)

Tumours were discovered in the right eye at the age of 3 years, and in the left at the age of 4½ years. Both eyes were subsequently enucleated at the Glasgow Royal Infirmary, and the lesions were diagnosed as 'retinal gliomata'. No further treatment was necessary, and the patient is still alive and well and living in Scotland. Detailed inquiries revealed no history of similar disease among the grandparents, parents, siblings, or any other relatives.

CASE 2

(II/1, male, born 1921, the eldest son of Case 1)

At the age of 3 years, the left eye was noted to have 'changed colour', taking on a 'blank' appearance. Examination revealed a white tumour projecting into the vitreous and the eye was enucleated. Three years later, after the discovery of a similar lesion, the right eye was also removed. No further treatment was given, and the patient has had no local or systemic recurrence.

CASE 3

(II/2, male, born 1923, the second son of Case 1)

A tumour was discovered in the left eye on routine examination at the age of 6 years. The eye was subsequently enucleated, histological investigation confirming the diagnosis of retinoblastoma. No further treatment was required. The right eye is unaffected, and the patient is still a keen and accurate pheasant shooter.

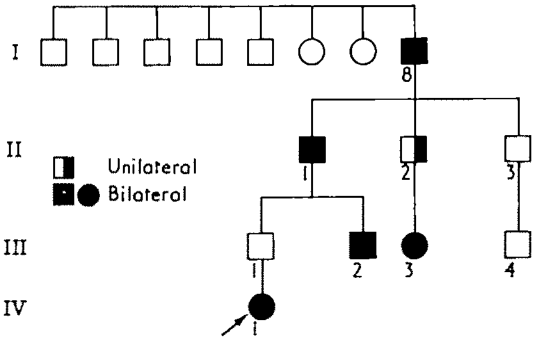

FIGURE *Pedigree of family reported with retinoblastoma occurring in four successive generations*

Conventional symbols are used: squares indicate males; circles females

CASE 4

(III/1, male, born 1949, the elder son of Case 2)

No eye disease was evident. The fundus was normal, with no evidence of retinal changes indicating spontaneous regression of retinoblastoma; however, this man's child had bilateral retinoblastoma, see Case 7.

CASE 5

(III/2, male, born 1955, the younger son of Case 2, and the younger brother of the previous case)

At a routine check, a tumour was discovered in the left eye at the age of 3½ months; the eye was then enucleated. Retinoblastoma was also discovered in the right eye at the age of 9 months; this was treated with radiotherapy. Follow-up examinations revealed no recurrence of the tumour in the right eye, while the left socket remained clear. Visual acuity in the right eye was normal.

CASE 6

(III/3, female, born 1954, the only child of Case 3)

Tumours were noted in both eyes at the age of 1 year, and these were treated with radiotherapy. The tumour in the right eye responded well, but the tumour in the left, which was close to the optic nerve head, retrogressed, and the eye had to be enucleated. Histological examination confirmed the presence of retino-

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*Present address: Department of Ophthalmology, Groote Schuur Hospital and Observatory, Cape Town, South Africa

Address for reprints: Dr C. Migdal, Department of Ophthalmology, Groote Schuur Hospital and Observatory, Cape Town, South Africa

blastoma. A sequel to treatment has been the development of a minimal postirradiation cataract in the right eye.

CASE 7

(IV/1, female, born 1973, the only child of Case 4, himself not affected with retinoblastoma)

Routine examination under general anaesthesia at the age of 1 year revealed the presence of bilateral retinoblastoma. The tumour in the right eye was 3 mm in diameter, and situated just above the macula. The small tumour in the left eye was near the optic disc. The child was otherwise well. Both tumours were treated with the Xenon arc laser. At follow-up examinations during the course of 5 months until the time of writing, the tumours appeared inert, with no evidence of new primary tumours. The child will continue to be examined at regular intervals.

Discussion

This family with retinoblastoma is of interest because the tumour has occurred in four successive generations.

Two forms of retinoblastoma are encountered, namely sporadic and familial. A brief résumé of the disease pattern of these tumours follows:

Sporadic cases

These are cases in which there is no family history of the disease.

Sporadic cases may, in turn, be divided into somatic and germinal mutants.

Somatic mutants

As the genetic abnormality is in the retina itself, the disease is not transmitted to the offspring. Only one eye is affected.

Germinal mutants

The genetic abnormality lies in the germinal epithelial cells of the gonads of one parent (who is clinically normal), with the result that the mutation is passed on to the next generation by the gametes. The disease is usually bilateral.

Knudson (1971) has put forward the hypothesis that retinoblastoma is a tumour caused by two mutational events. In the dominantly inherited form, one mutation is inherited *via* the germinal cells, and the second occurs in somatic cells. In the non-hereditary form, both mutations occur in somatic cells.

Familial cases

The familial group of cases exhibit autosomal dominant inheritance with incomplete penetrance (François and van Leuven, 1964). An affected individual has a 40–45 per cent chance of producing affected children (Warburg, 1974). Direct transmission is usual, but a generation may be skipped, while the disease occurs in collateral lines (Macklin, 1959).

In family groups, there is, in addition to phenotypically affected members, a percentage of carriers. It should be noted that some carriers show evidence of spontaneous tumour regression, while others (as in the reported family), do not.

Summary

Retinoblastoma occurring in four successive generations is described, followed by a brief discussion on the mode of inheritance of these tumours.

I am deeply indebted to Mr M. A. Bedford, Consultant Ophthalmologist at St Bartholomew's Hospital, for his encouragement and support, and for his permission to publish particulars of these cases.

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A method of artificial eye manufacture

HELENE JAMES, JEAN R. ELLIS, AND WALLACE S. FOULDS
From the Tennent Institute of Ophthalmology, University of Glasgow, and Glasgow Eye Infirmary

In most hospitals in the United Kingdom and in many other countries, the provision of an artificial eye depends upon an exchange of information between an artificial eye fitter and an artificial eye manufacturer who may be situated some distance away and who, in most instances, does not see the patient. The centralization of manufacturing facilities may have some advantages and while, in general, the transfer of information between fitter and manufacturer results in an adequate prosthesis, there are inherent difficulties not only in the accurate interpretation of the fitter's instructions but also in relation to the commonly used methods of manufacture. Because of these difficulties, a modified method for the production of artificial eyes has been developed in Glasgow by one of us (HJ) and it is thought that the results obtained by this method justify its being more widely known.

The information transmitted to the manufacturer by a fitter will usually include a wax model of the prosthesis into which a plastic disc has been set to indicate the position of the iris and pupil (Fig. 1), together with written instructions about the colour and texture of the iris, the colour of the sclera, and the presence and pattern of vascular markings and other discolourations.

The main bulk of the artificial eye is manufactured to conform with the wax model. A circular hole is drilled into its anterior surface to take a painted plastic disc representing the iris and subsequently a clear acrylic cornea is added anteriorly (lensing) after the addition of vascular and other markings to the sclera.

The problems with this method are first, that the manufacturers are at a great disadvantage in never having seen the patient for whom the eye is being prepared. They must rely upon the interpretation of possibly ambiguous instructions, for qualitative information about the patient's normal eye is difficult to convey in writing. It is upon a combination of many small details that the appearance of an artificial eye depends and a perfect colour match of the iris, for example, can be spoiled completely by too much or too little in the way of vascular markings on the related sclera.

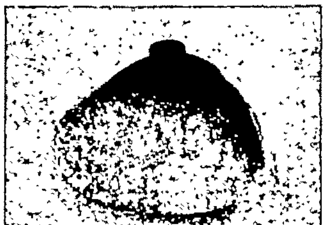

FIG. 1 *Wax model of prosthesis used in conventional artificial eye manufacture with embedded plastic disc which marks position of iris. Central protrusion indicates position of pupil*

The second problem with the usual method of manufacture is a possible inaccuracy in the position of the iris resulting from difficulty in placing the plastic former accurately on the wax model. The small central protrusion upon the plastic former which marks the position of the pupil may on occasion foul the upper lid margin making accurate centration difficult (Fig. 2). A further inaccuracy may result from slight errors in boring into the half-made prosthesis. An iris misplaced because of this, needs only to be a little

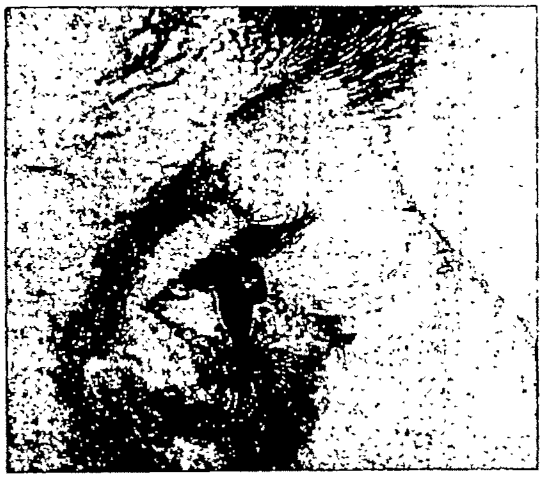

FIG. 2 *Conventional wax model* in situ. *Central protrusion may foul upper lid making centration difficult*

Address for reprints: Professor W. S. Foulds, 3 The University, Glasgow G12 8QG

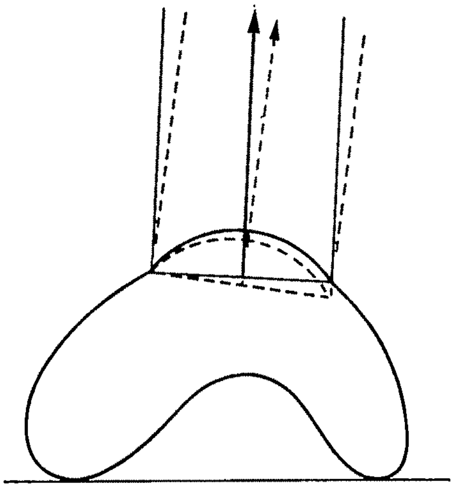

FIG. 3 *Diagram to illustrate how slight eccentricity in drilling bed in prosthesis for insertion of iris disc may alter the 'gaze' of artificial eye and necessitate major modification of prosthesis*

out of true to require major alteration to the shape of the artificial eye to rectify it (Fig. 3).

In an attempt to circumvent these problems, it was decided to have the artificial eye fitter not only to fit the prosthesis but to manufacture it as well. As most of the materials and techniques used in the manufacture of artificial eyes originate in dentistry, it was decided to adapt the method whereby the bulk of the dentures is added to the teeth, and to try to add the sclera to the iris rather than *vice versa*. Thus the iris is painted with direct reference to the colour and pattern of the remaining eye and the painted iris disc is 'lensed' with its clear acrylic cornea in a specially constructed flask (Fig. 4) as the first stage in the production of the prosthesis. A mould of the patient's socket is taken in the conventional manner and a wax model of the mould prepared. The combined iris and cornea is then inserted into this wax model in place of the conventional plastic disc used to achieve centration of the pupil and iris, and the position of the iris is modified until it is satisfactory.

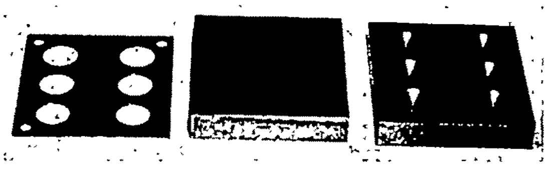

FIG. 4 *Special flask used to 'lens' previously painted iris discs. Discs themselves are prepared using same flask substituting flat surfaced base for base with corneal indents illustrated*

A small blob or projection of rapidly polymerizing acrylic is added to the apex of the cornea before the wax model with its embedded iris and cornea is inserted into wet plaster-of-Paris in a compress flask. When the plaster has set, the wax is carefully removed leaving the painted iris and cornea held in place by the added projection which is gripped by the plaster (Fig. 5).

The space in the mould previously occupied by the wax is filled with monomer and catylist mixed to match the colour of the fellow sclera and the prosthesis is then heat cured.

The artificial eye complete with iris and cornea is taken from the flask and the projection removed from the cornea. A thin layer of acrylic, mixed to the required sclerotic shade, is spread over the cornea and heat cured. By carefully sandpapering this layer one can reproduce the gentle merging of the cornea with the sclera at the limbus seen in the normal eye and eliminate the harsh outline of the limbus which mars so many prostheses. Other effects, such as an arcus senilis or some degree of lens opacity, can also be reproduced at this stage by appropriate removal of the acrylic layer which has been applied over the cornea.

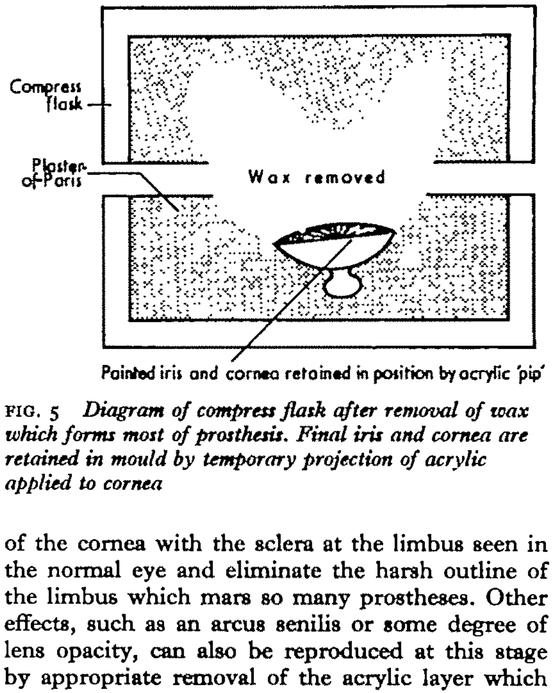
Compress flask
Plaster-of-Paris
Wax removed
Painted iris and cornea retained in position by acrylic 'pip'

FIG. 5 *Diagram of compress flask after removal of wax which forms most of prosthesis. Final iris and cornea are retained in mould by temporary projection of acrylic applied to cornea*

When the appearance of the iris and cornea has been modified to match the patient's remaining eye, the scleral surface is reduced by 1–2 mm, and vascular markings and stains on the sclera are added to match those of the fellow eye. At this stage the fitter who suspects that further adjustment to the anterior surface of the prosthesis might be required after a short period of wear, can remove a thicker layer of acrylic from the critical positions; thus alteration to the anterior surface of the finished prosthesis, if required, will not remove any of the vascular markings.

The layer of sclera thus removed is replaced by a mixture of clear acrylic resin which is polymerized and the eye is then finished by polishing.

In certain cases, for example in patients with microphthalmic eyes, the impression of the socket is translated directly into an acrylic trial shell in the manner of a contact lens fitting. The patient wears this for a week to establish the comfort and accuracy of the fit, and then sufficient acrylic is removed from the anterior surface of the trial shell to enable a painted iris and cornea to be affixed with wax. The appearance of the eye is then checked in the patient's socket. Any necessary modifications to the anterior planes of the prosthesis are executed by the addition of wax or the removal of acrylic. The manufacture then proceeds in the usual manner, with the exception that the wax surrounding the painted iris and cornea is softened by pouring hot water on to the trial shell to enable it to be removed from the compress flask, leaving the iris and cornea in position in the mould.

The advantages of using this method are that the iris colour can be checked by the fitter/maker and also by the patient at an early stage of manufacture. As in all cosmetic effects, personal taste enters into the satisfaction of the wearer and, curiously, some patients prefer their artificial eye to be slightly darker, some slightly lighter, than their own. By inserting the painted iris into the wax model, the patient can have a much closer impression of what the finished eye will look like. It is impossible to obtain the patient's reaction to the appearance of the prosthesis at the fitting stage, when alterations are most easily made, if the conventional blank plastic disc is used in place of the iris.

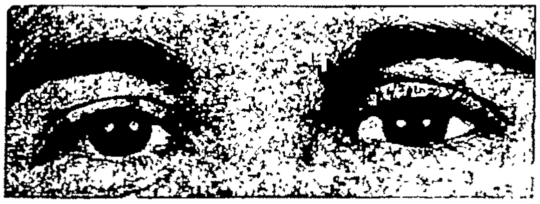

FIG. 6 *A satisfactory prosthesis*

When the fitter paints and makes the eye, close attention can be paid to the small details which contribute so largely to the final effect, and care can be taken that the vital planes and curves of the shape are not lost by over enthusiastic polishing at the final stage. Certainly the fitter who also makes the eye must have artistic skill and a good colour sense, and he must take total responsibility for the final product. This, however, adds considerably to the satisfaction both from the patient's and fitter's point of view when a successful fitting is achieved (Fig. 6).

We wish to acknowledge the help of Mr W. Jones, Instrument Technician in the Tennent Institute of Ophthalmology, in relation to the manufacture of the metal flasks. We should also like to thank Mr J. Watt, Chief Technician, and his staff for the photography.

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Book reviews

Eye Muscle Problems in Childhood. A Manual for Parents. By C. E. WINDSOR and J. HURTT. 2nd ed. 1974. Pp. 48, 18 figs. Mosby, St Louis; Kimpton, London (80p)

This book provides a concise and factual account of the problems which beset disorders of ocular motility, particularly those developing in early childhood. It is designed for the guidance of the parents of such children, and represents a revision and condensation of the monograph *Strabismus in Childhood* by Herbert M. Katzin and Geraldine Wilson which appeared in 1968 and which was based on the book *Rehabilitation of the Child's Eyes* by Richard Scobee.

The book deals with the mechanisms which are concerned in the development of normal binocular function and with the defects which are liable to interfere with this process so that there is the production of a squint. This sequence provides a ready explanation for the various motor and sensory disorders which form part of the squint and also a basis for the methods of treatment which are adopted to secure a satisfactory functional result. It is almost tedious to find fault with the text which is largely uncontroversial and represents an up-to-date approach to the whole subject, but it is marred by the statement that the retina becomes fully developed and sensitive enough to register focused images only between the ages of 2 and 3 years and also by the statement that the lack of development of an infant's eyes accounts for the type of convergent squint which usually disappears within the first 8 months. Surely these remarks belong to a bygone age, and in any event are refuted in other parts of the text which stress the need for an early assessment in all cases of suspected squint. KENNETH WYBAR

The Eye and Systemic Disease. Edited by A. MAUSOLF. 1975. Pp. 450, figs, tables, refs. Mosby, St Louis; Kimpton, London (£21·75)

This publication presents a series of papers given at a symposium organized by the Department of Ophthalmology, Iowa City 1974. In 400 pages the major fields of medical ophthalmology are extensively and refreshingly covered. Each subject under discussion combined papers by a physician and an ophthalmologist, both of whom were accredited experts in their chosen fields. The expertise collected in this way provided interesting discussion periods which are fully reported. These factors serve to make this book one of the most authoritative books on the eye and systemic disease.

Hereditary metabolic diseases were discussed by Fredrickson whose contributions to this subject are already well known, and his ophthalmological partner Podos provided a comprehensive review of the ocular signs to make this a powerful opening for the symposium. An interesting paper by Ditzel from Denmark discussed disordered oxygen transport by the red cell in diabetics with assessment of 2·3—DPG (2 3—diphosphoglyreate), and this was paired by an interesting review of the ocular signs by Henkind. Almost a quarter of this book is devoted to dermatology and the eye, with extensive systemic (Perry) and ophthalmic (Bietti) coverage. Other topics discussed include collagen diseases and the eye (Kearns), vascular disease (Cogan), gastrointestinal disease (Knox), endocrine disease (Dardenne), blood and reticulo-endothelial disease (Luxembourg), and nutritional disease (Halasa).

The book is beautifully produced, well edited, and contains a most extensive bibliography. It seems a necessary purchase for any ophthalmologist concerned with the wider implications of ophthalmic diagnosis and treatment. M. D. SANDERS

Helfer des Augenarztes (The Ophthalmologist's Assistant). By KARL VELHAGEN. 1974. Pp. 287, 136 figs, 11 tables, refs. Thieme, Leipzig (DM43·20)

As the title suggests this is a book not so much for the ophthalmologist but for his assistant. It deals with the large variety of tests and procedures that are linked with routine ophthalmic practice. There are chapters on anatomy, basic physiology and optics, but the major part of the book is concerned with the carrying out of single diagnostic techniques and nursing procedures. The ophthalmic assistant in most Continental countries fills the role of receptionist, nursing sister, technician, and secretary and this book is intended as a working manual and vade-mecum.

Unfortunately this type of ophthalmic assistant rarely exists in England but this volume, if it were translated, would be an excellent addition to nurses' libraries, and to the practical manuals found in ophthalmic outpatients and casualty departments.

T. J. FFYTCHE

Ocular Manifestations of Inborn Errors of Carbohydrate and Lipid Metabolism (Bibliotheca Ophthalmologica No. 84). Edited by J. FRANÇOIS. 1975. Pp. 175, 85 figs, 3 tables, refs. Karger, Basel (DM74)

It is a pleasure to see this brief, and excellent monograph by one of Europe's most prolific contributors. The subject is one of increasing complexity as biochemical and histological studies continue to define subgroups of the previously well defined clinical syndromes.

The book is divided into three sections on: carbohydrate metabolism, lipid metabolism, and the mucolipidoses.

Reference is made only to those disorders that involve the visual system, and in particular, the sensory system.

The text is clear and amplified by numerous illustrations but the bibliography, although considerable, lacks many important recent references. The English is excellent although terms such as dysoric retinopathy (page 87) might elude the most knowledgeable reader. This book obviously suffers from certain disadvantages when an ophthalmologist enters such a complex and changing field. There is thus confusion between Batten-Mayou disease and juvenile GM_2 gangliosidosis, and the complex subject of Niemann-Pick disease could be clarified. The author states that the enzymatic defect of Farber's disease is not known although it was described in 1972.

However, the condensation of information into 173 pages is appealing, and this book is strongly recommended for ophthalmologists as a practical way to keep abreast of this exciting field. M. D. SANDERS

Ocular Pharmacology. By W. H. HAVENER. 1974. 3rd ed. Pp. 715, figs, tables, refs. Mosby, St Louis; Kimpton, London (£18·30)

This book is drug orientated. Three-quarters of it is devoted to basic pharmacology and the wider use of drugs in ophthalmology. In the remainder current therapy is considered primarily in connection with cataract and glaucoma.

The book is essentially on applied physiology and pharmacology and written by a clinician for clinicians. Most aspects are covered fairly comprehensively with extended chapters on antibiotics, autonomic drugs, and steroids.

In an early general section emphasis is placed on avoiding unnecessary, useless, and wasteful prescriptions and the possibility of serious side-effects of drugs. We are reminded that among contraindications for the use of a drug is often the lack of its specific indication.

The author has a pleasing style and does not hesitate to add his own views. From time to time a point is reinforced with an interesting or amusing anecdote.

D. GREAVES

Symposium on Ocular Therapy, Vol. 7. Edited by I. H. LEOPOLD. 1974. Pp. 134, tables, figs, refs. Mosby, St Louis; Kimpton, London (£10·20)

The contents of this book are not quite what would be expected from the title, as the account is more on the complications of drugs than their beneficial effects, but this adds to rather than detracts from the usefulness of the volume.

It is estimated that 2 to 3 per cent of all congenital malformations are induced by drugs or environmental chemicals, and the first chapter contains a comprehensive review of the ocular lesions induced by drugs taken during pregnancy. The problems arising from drug interactions and individual susceptibility are next briefly discussed, and these chapters are followed by a long discussion of the diagnosis, pathogenesis, surgical and medical treatment of neovascular glaucoma. In spite of the many procedures suggested, the prognosis for vision is very poor and the best that can be done is to relieve pain.

Vitreous haemorrhage is not amenable to any medical treatment, and a critical analysis of the results of corticosteroid therapy in acute optic neuritis concludes that it is of no benefit. The final chapters contain a brief discussion on prostaglandins and the eye, and the use of aspirin and other prostaglandin synthetase inhibitors in ophthalmology, and a brief review of drug-induced retinopathies.

Although the reader will find no magic drug to enhance his therapeutic potential, he will at least be warned of the dangers inherent in the use of drugs and be more aware of their toxic effects. E. S. PERKINS

Ultrasonography in Ophthalmology (Proceedings of the Fifth Congress of the International Society for Ultrasonic Diagnostics in Ophthalmology, Ghent, 30 May, 1973). Edited by J. FRANÇOIS and F. GOES. 1974. Pp. 340, 66 tables, 172 figs, refs. Karger, Basel (£25·60)

The reports have been split into four sections dealing in turn with techniques, intraocular and orbital diagnosis, and oculometry.

In a series of communications, scanning was shown to be a useful tool in the diagnosis of vitreous haemorrhage and in excluding or confirming any underlying cause such as tumour or detachment. Similarly, scans may help to differentiate a solid from a fluid or simple detachment. Articles on intraocular foreign body and tumour localization by scanning, and evidence deduced concerning optic nerve and orbital pathology could be of assistance to the surgeon. The possibility of tissue differentiation and ultrasonic velocity change, as seen in cataract, was being explored experimentally as well as from the research point of view. Oculometry was used for measuring anterior chamber depth, eyeball length in myopia and the calculation of dioptric power for acrylic lens implants after cataract extraction. The last paper showed that the method had been helpful in noting changes in lens and anterior chamber size with the use of drugs.

This book is a useful addition to the literature on ultrasonics and follows as a natural companion to the report of the previous congress. The many diagrams and figures allow the book to be easily read and understood by the beginner. It will be a handy reference book for workers in the field and is to be recommended.

G. V. CATFORD

Brit. J. Ophthal. (1976) **60**, 158

Correspondence

Pathogenesis of cupping of the optic disc

TO THE EDITOR *British Journal of Ophthalmology*

SIR, Professor Hayreh has performed a great service in reiterating the ischaemic nature of optic disc cupping and of the particular susceptibility of the prelaminar tissue and peripapillary choroid to imbalance between the intraocular pressure and local perfusion pressure (Hayreh, 1974a). I would disagree with him, however, that the atrophic cupping seen after temporal arteritis is 'identical in all aspects' to that seen in glaucoma and low-tension glaucoma. Since the occurrence of cupping in temporal arteritis was first brought to my notice at the Oxford Congress in 1972 (Miller, 1972) I have been looking at my cases for this and have, indeed, found cupping not infrequently. I assume that Professor Hayreh is referring to the clinical appearance of the discs and not to other clinical details such as the complete loss of vision or gross altitudinal loss in the one compared to the usual presence of good vision, apart from typical scotomata, in the other. No one is likely to confuse them clinically and it may be on this account, as well as its rather tardy development in many cases, that its occurrence in temporal arteritis has previously been practically overlooked. But there are some differences in ophthalmoscopic appearance, especially before the intraocular pressure has been normalized. The glaucomatous cup is of a darker grey especially where it reaches to the edge of the disc, which it usually does only in parts (above and below), except in cases where it is very advanced and there are other signs such as displacement of vessels against the nasal wall of the cup. In early cases there may also be fullness of veins. The cupping I have seen in temporal arteritis, and only in about half of my cases, is of a paler grey, reaching the edge all round unless a sector of field is spared without any particular displacement of vessels, and with a general attenuation of vessels. It is what is called 'atrophic cupping' and this is a useful term to distinguish it from glaucomatous cupping.

I had hoped Hayreh, 1974b, might elucidate these points, and also that the paper would give the incidence of cupping. However, the table and figure were the same in both papers, and one cannot elucidate the incidence as there were 13 eyes, some bilateral, out of 25 cases. Please could he put the record straight.

Yours faithfully,
JOHN PRIMROSE

Regional Eye Centre,
Oldchurch Hospital,
Romford, Essex

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HAYREH, S. S. (1974a) *Brit. J. Ophthal.*, **58**, 863
——— (1974b) *Ibid.*, **58**, 964
MILLER, S. J. H. (1972) *Trans. ophthal. Soc. U.K.*, **92**, 563

Pathogenesis of cupping of the optic disc

TO THE EDITOR *British Journal of Ophthalmology*

SIR, I should like to thank Mr John Primrose for confirming the occurrence of cupping of the optic disc in temporal arteritis, not only found by me but also reported by Mr S. J. H. Miller in his Doyne Memorial Lecture at the Oxford Congress in 1972. However, I disagree with Mr Primrose in his other statements. The clinical ophthalmoscopic appearance of the optic disc cupping seen in temporal arteritis is very similar to that seen in chronic simple glaucoma and low-tension glaucoma with cupping usually maximal in the temporal part of the optic disc and with nasal displacement of the main retinal vessels. This is evident from Fig. 2d (Hayreh, 1974) and Mr Miller agreed with me in the observation. I feel the degree of greyness mentioned by Mr Primrose is irrelevant and of no practical significance because there is a considerable variation in the greyness seen in different discs in both glaucoma and temporal arteritis. He has made no mention of the exact incidence of 'darker grey', or 'paler grey' (both of which descriptions are subjective) or of the absence of greyness in optic disc cupping in glaucoma and, it seems, that he has made his statement purely on so-called 'clinical impressions' derived from routine ophthalmoscopy which a scientific study might reveal to be without statistical significance. In my studies I personally photographed on Kodachrome II colour films with a stereoscopic fundus camera the optic discs of every patient with temporal arteritis, and my observations were based on stereoscopic examination of these discs at a standard illumination; this method provides a considerable amount of information which is not usually obtained by routine ophthalmoscopy with variable illumination.

I feel Mr Primrose's concept of 'atrophic cupping' is not what is classically known in ophthalmology. As is well known, this is seen in marked optic atrophy and consists of a very shallow saucer-shaped or flat depression (not a cup) involving the optic disc, without any steep edges or nasal displacement of the main retinal vessels. Histopathologically, in 'atrophic cupping' there is a destruction of nerve fibres only, without any loss of glial cells; whereas in glaucomatous cupping (and also in temporal arteritis) there is ischaemic destruction of both the nerve fibres and the glial cells in the prelaminar part of the disc. Thus to describe cupping of the optic disc in temporal arteritis as 'atrophic cupping' would not only be erroneous but also misleading.

I have given the incidence of optic disc cupping in the table mentioned by Mr Primrose. The incidence pertains to the number of eyes in my series and not the cases; I feel the latter is irrelevant as we are interested in finding the incidence of the cupping in the eyes affected by temporal arteritis and not in the cases, since every patient with temporal arteritis does not have both eyes involved and sometimes no ocular involvement at all. Thus any mention of incidence of cupping of the disc in patients would be misleading.

Yours faithfully,
SOHAN S. HAYREH

The University of Iowa
Department Ophthalmology,
Iowa City,
Iowa, USA

Reference

HAYREH, S. S. (1974) *Brit. J. Ophthal.*, **58**, 968

Anterior ischaemic optic neuropathy

TO THE EDITOR *British Journal of Ophthalmology,*

SIR, I should like to thank Dr Sohan Singh Hayreh for calling attention to my annual review of neuro-ophthalmology (Lessell, 1974). In it the reader will find that I devoted a paragraph to several of Dr Hayreh's many excellent studies on anterior ischaemic optic neuropathy (AION) (Hayreh, 1974). Dr Hayreh cavils at my comment that there are obvious differences between spontaneous human AION and the AION that is produced in monkeys. Regardless of whether or not I was correct in my observation, these differences are only of secondary importance and do not detract from Dr Hayreh's convincing demonstration of the central role of the posterior ciliary arteries in the pathogenesis of AION. Dr Hayreh also accuses me of making a misleading and dangerous statement concerning the differential diagnosis of optic atrophy. However, I neither stated nor implied that metastatic tumour was a more common cause of optic atrophy than AION. What I wanted to convey was that if you observe a patient throughout the course of his illness (including the acute phase) and at no time is optic disc oedema observed, you should be dubious of the diagnosis of AION.

Dr Hayreh and I probably hold very similar views on AION. Perhaps this letter will make that apparent. In any case, a reading of my review (Lessell, 1974) and the relevant papers of Dr Hayreh (Hayreh, 1974) should show that there is no foundation for serious controversy.

Yours faithfully,

SIMMONS LESSELL

Boston University School of Medicine,
80 East Concord Street,
Boston,
Massachusetts, USA

References

HAYREH, S. S. (1974) *Brit. J. Ophthal.*, **58**, 955, 964, 981

LESSELL, S. (1974) *Arch. Ophthal.*, **91**, 166

Notes

Pan-Hellenic Ophthalmological Congress

Thessaloniki, 28 *to* 30 *May* 1976

The ninth congress will be held in Thessaloniki, Greece. The subjects will be: Steroids and antibiotics in ophthalmology, Surgery of the lids, and Iatrogenic eye diseases.

There will be simultaneous translations in English and French.

For further information write to the Ophthalmological Society of North Greece, PO Box 497, Thessaloniki, Greece.

Canadian Ophthalmological Society

Quebec City, 6 *to* 9 *June* 1976

The 39th annual meeting will be held at the Quebec Hilton Hotel under the theme 'Medical aspects of the retina'.

Dr Pierre Almaric of Albi, France, and Dr H. Mackenzie Freeman of the Retina Association in Boston will be this year's special guests; they will present papers to the various scientific sessions.

Two half days will be devoted to discussions on the prevention of blindness, cataract, uvea, and surgical aspects of the retina. Research sessions will be held on Sunday, June 6, in the afternoon.

For further information write to the Canadian Ophthalmological Society, PO Box 8650, Ottawa, Ontario, K1G OG8, Canada.

The Eldridge-Green Lecture

London, 10 *June* 1976

The Eldridge-Green Lecture entitled 'The biological significance of optical illusions' will be delivered under the auspices of the Royal College of Surgeons of England by Professor R. A. Weale at 3 pm, at the Institute of Ophthalmology, Cayton Street (adjacent to Moorfields Hospital, City Road), London. Tickets are not required.

International Symposium of Fundus Fluorography and Photocoagulation

Scotland, 17 *to* 21 *October* 1976

The second symposium will be held at Gleneagles Hotel, Perthshire.

For further information write to Mrs Allene M. Gearce, Conference Secretary, Department of Ophthalmology, Ninewells Hospital and Medical School, Dundee DD2 1UB.

International Conference on Myopia

Yokohama, Japan, 10 *to* 12 *May* 1978

The main theme of the second conference will be acquired myopia and related problems.

For further information write to Tikasi Sato, MD, Sato Eye Clinic, Onoe-cho 6–90, Naka-ku, Yokohama, Japan (Zip Code 231).

Announcement

Retinitis Pigmentosa Foundation

The Retinitis Pigmentosa Foundation plans to take part in the establishment of one or more additional centres for the study of retinitis pigmentosa and of allied retinal degenerations. To that purpose the foundation will entertain centre or programme grant proposals for research support. In general, programmes should be directed towards a basic understanding of the gene defect or defects responsible for one or more types of hereditary retinal degeneration, or towards the acquisition of information on basic retinal function that is prerequisite to such an understanding. A detailed letter of announcement concerning this programme is available. Inquiries should be directed to Dennis Hartenstine, Executive Director Retinitis Pigmentosa Foundation, Rolling Park Building, 8331 Mindale Circle, Baltimore, Maryland 21207, USA.

Obituary

Hamilton Hartridge, MD, FRS

Hamilton Hartridge, Emeritus Professor in the University of London, died on 13 January 1976, aged 89 years. In more than one sense he was a colourful personality and made several significant contributions to physiology in general and sensory physiology in particular. His studies in visual physiology, for which he was largely known to an earlier generation, covered several fields. He was among the first to introduce physical principles to the analysis of visual acuity, and crucially demonstrated the role of the ciliary muscle in accommodation. Having relinquished the chair in physiology at St Bartholomew's Hospital – which he held from 1927 to 1947 – he came to the newly formed Institute of Ophthalmology as Director of the Vision Research Unit of the Medical Research Council. The Unit had been set up to give Hartridge a chance to test the polychromatic theory of colour vision which he had promulgated with few real experiments but many publications, including a special volume of the *Philosophical Transactions of the Royal Society*. From this point of view, the venture was a predictable disaster. Nevertheless, it was from that Unit that stemmed studies which gave the Institute such a standing in visual physiology as it may possess today. For better or for worse, this will be Hartridge's memorial.

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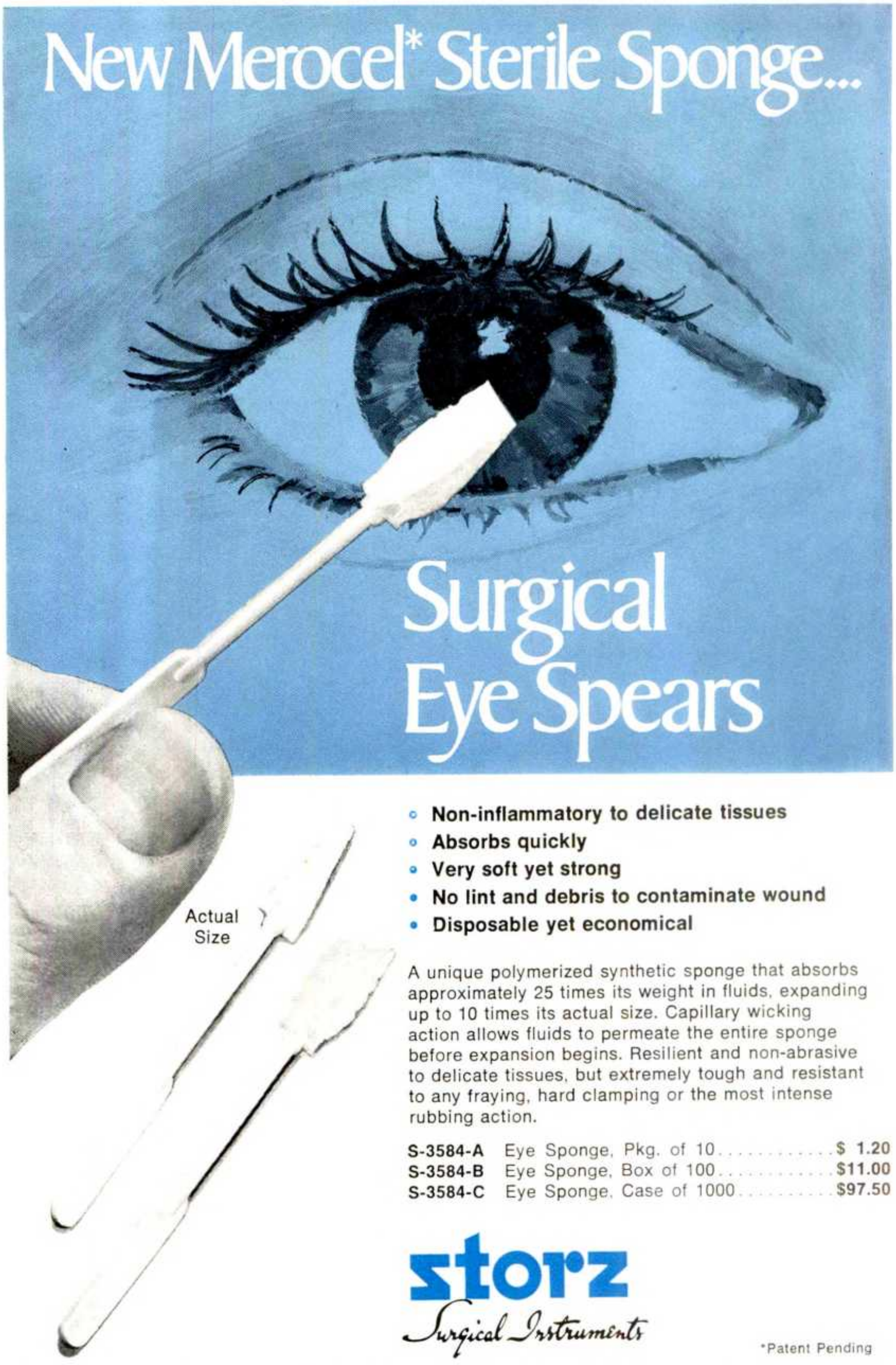

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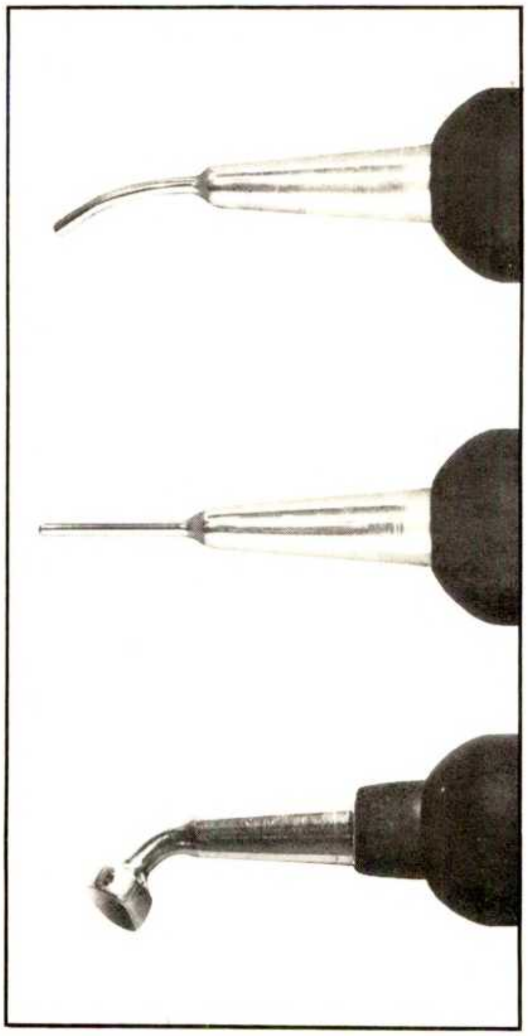

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Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Only recognized abbreviations should be used. Authors are asked to submit two copies of the text and references.

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COWAN, J. (1929) *Quart. J. Med.*, **22**, 237.

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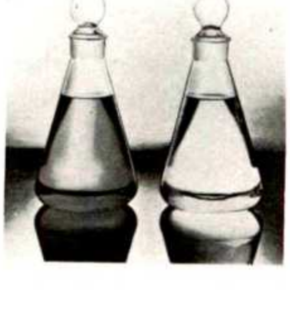

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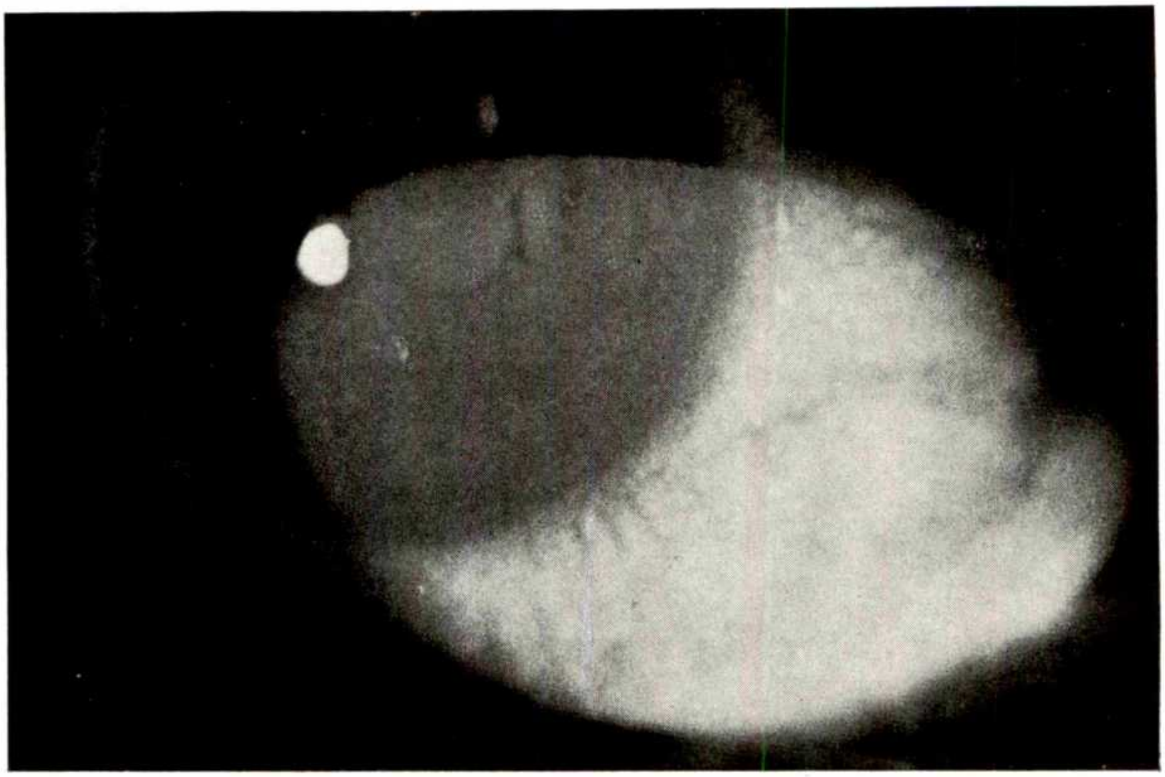

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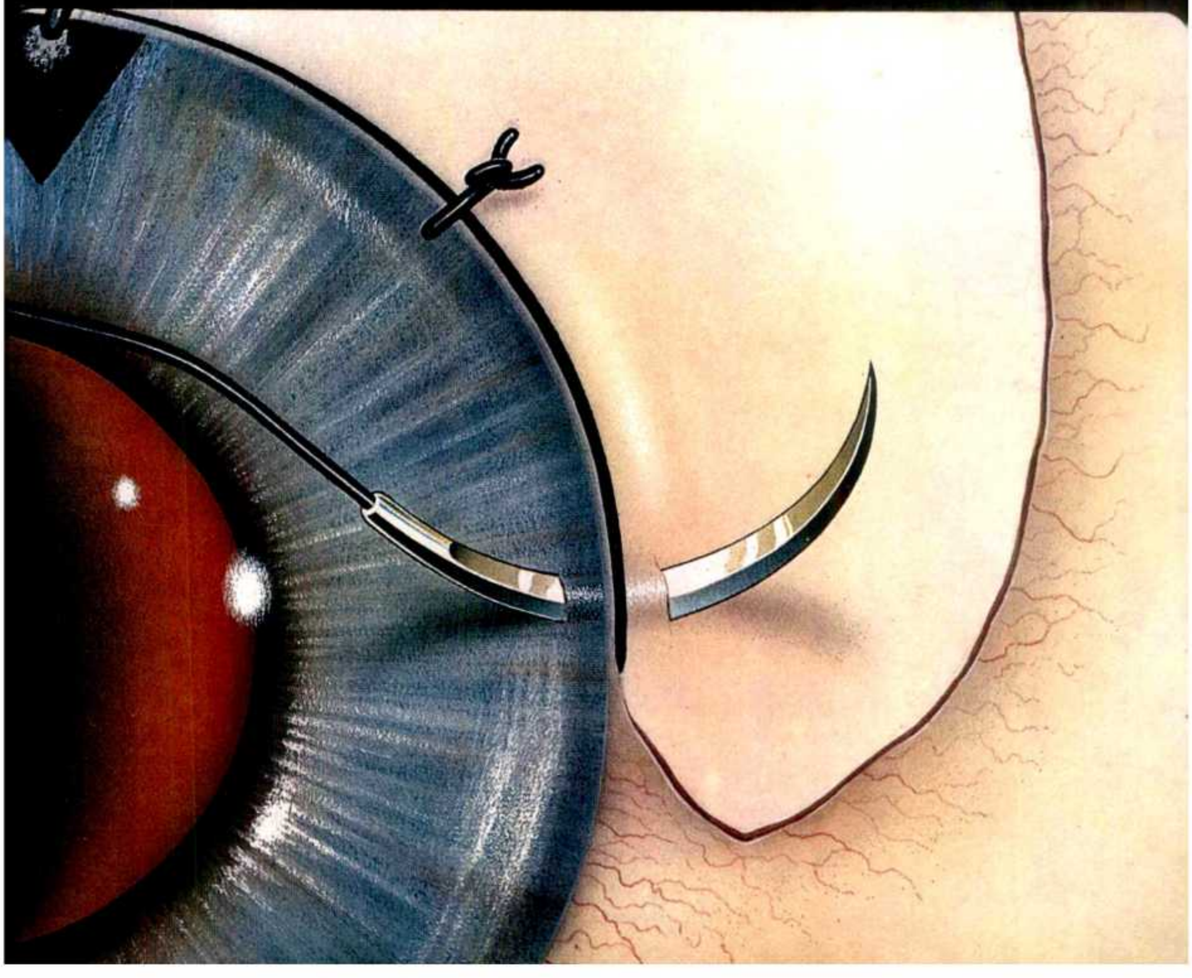

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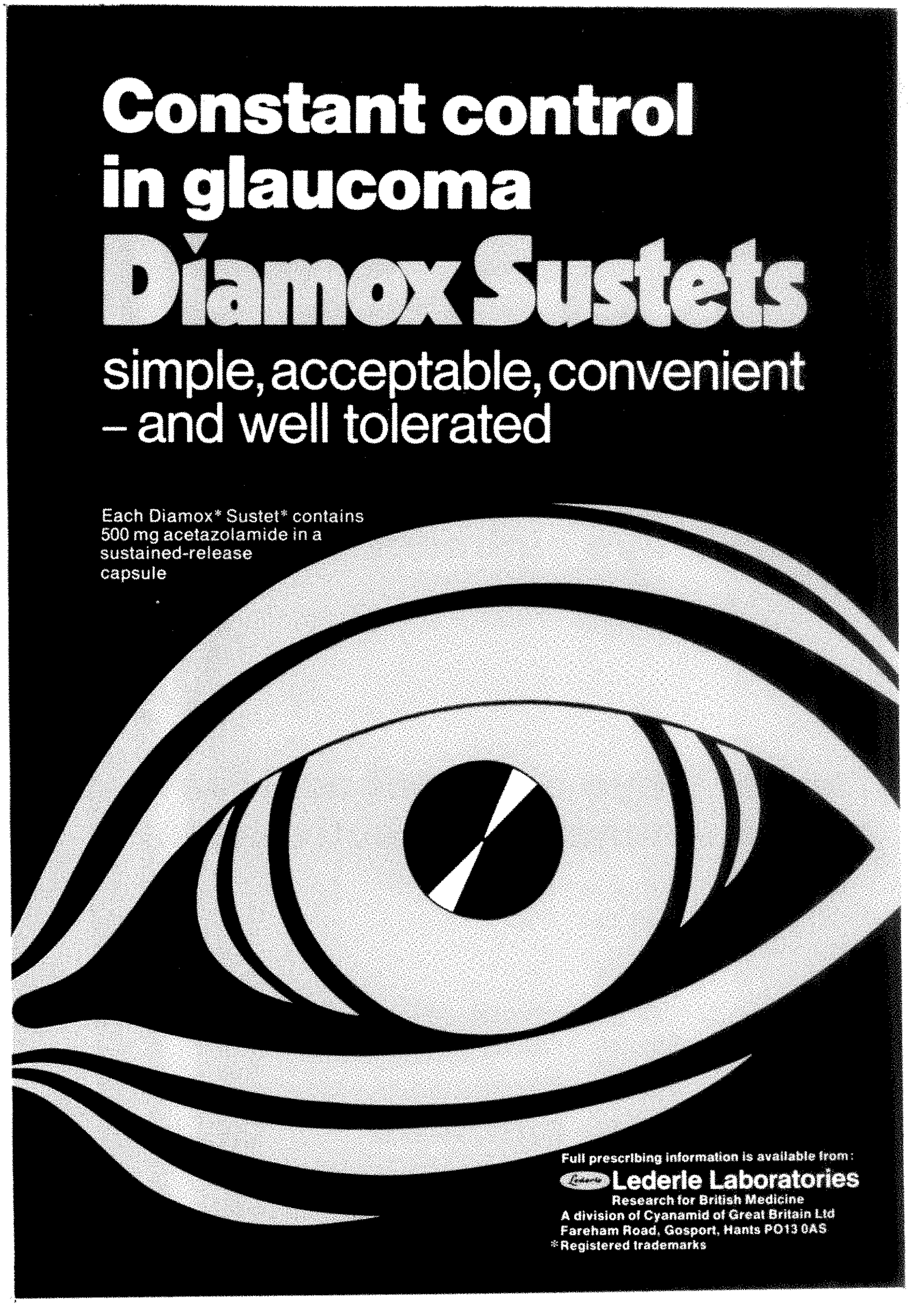

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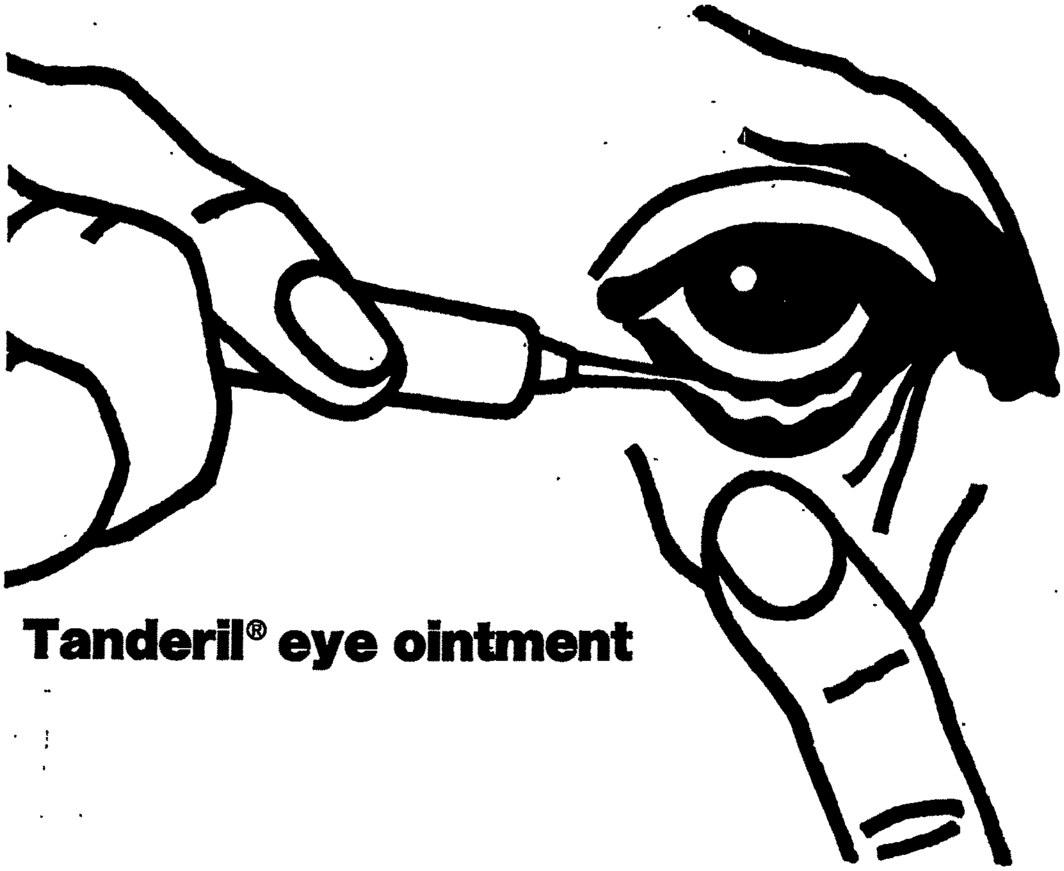

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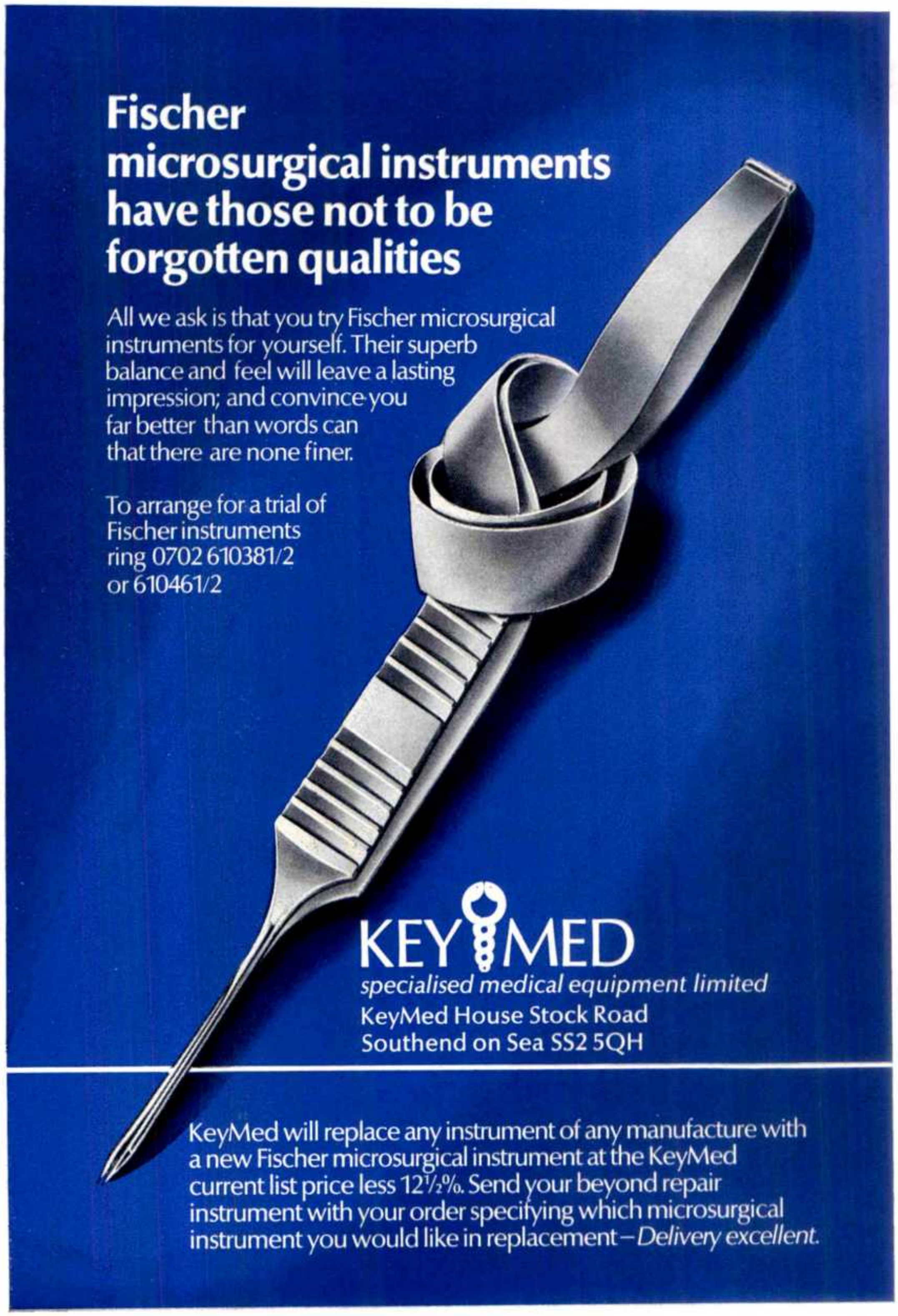

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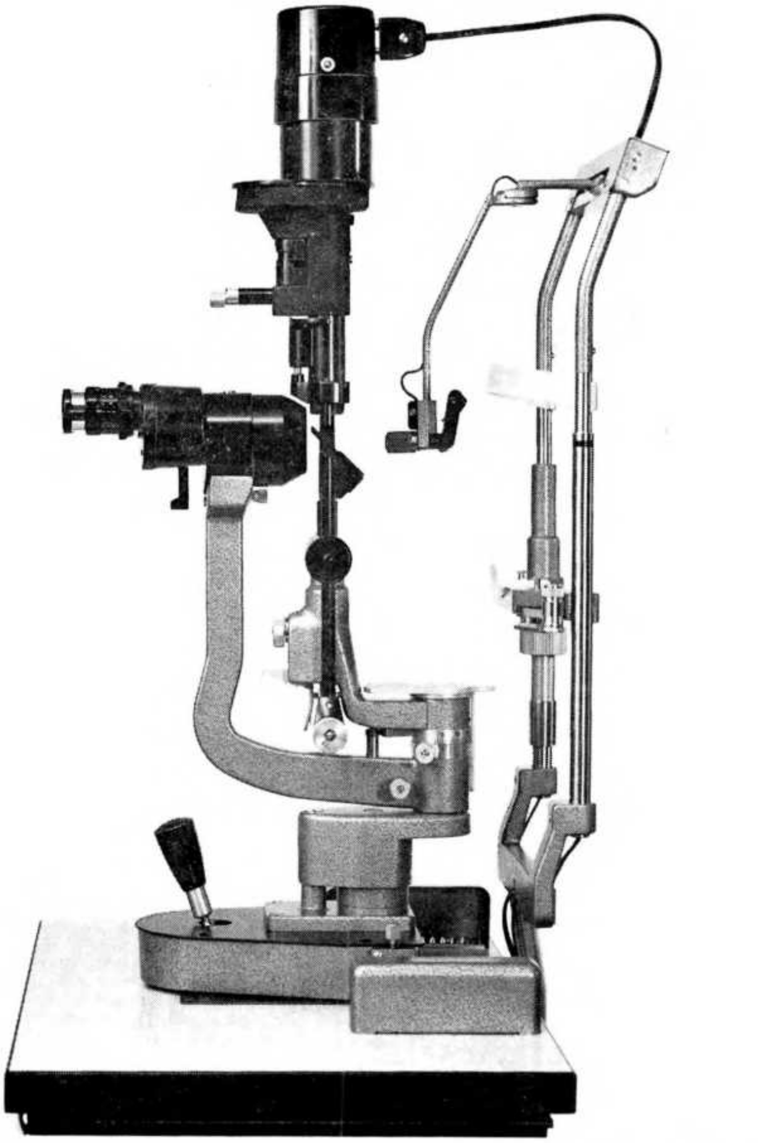

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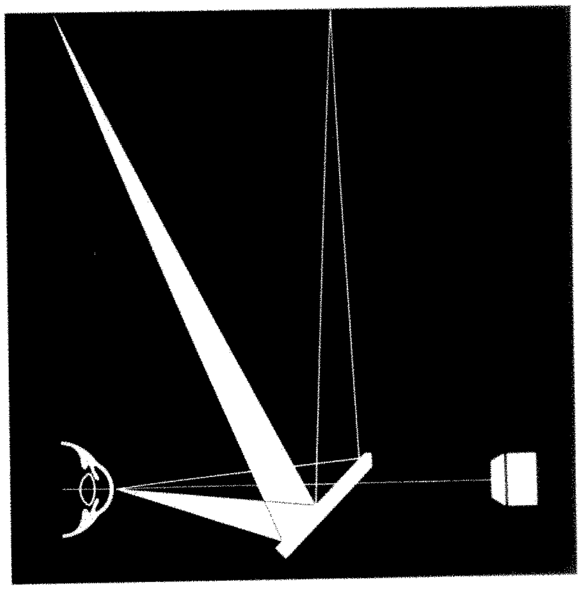

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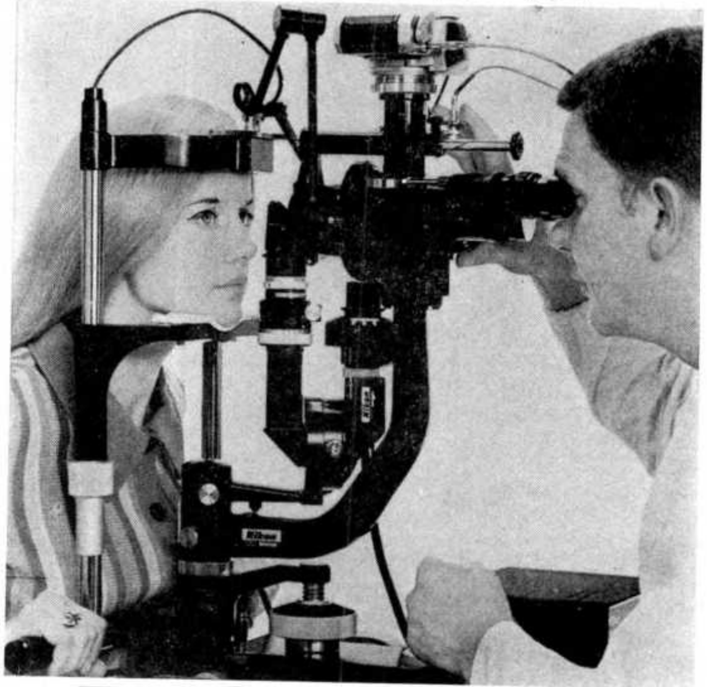

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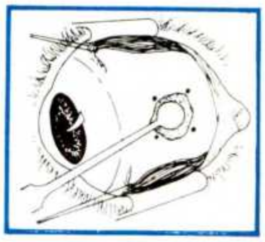

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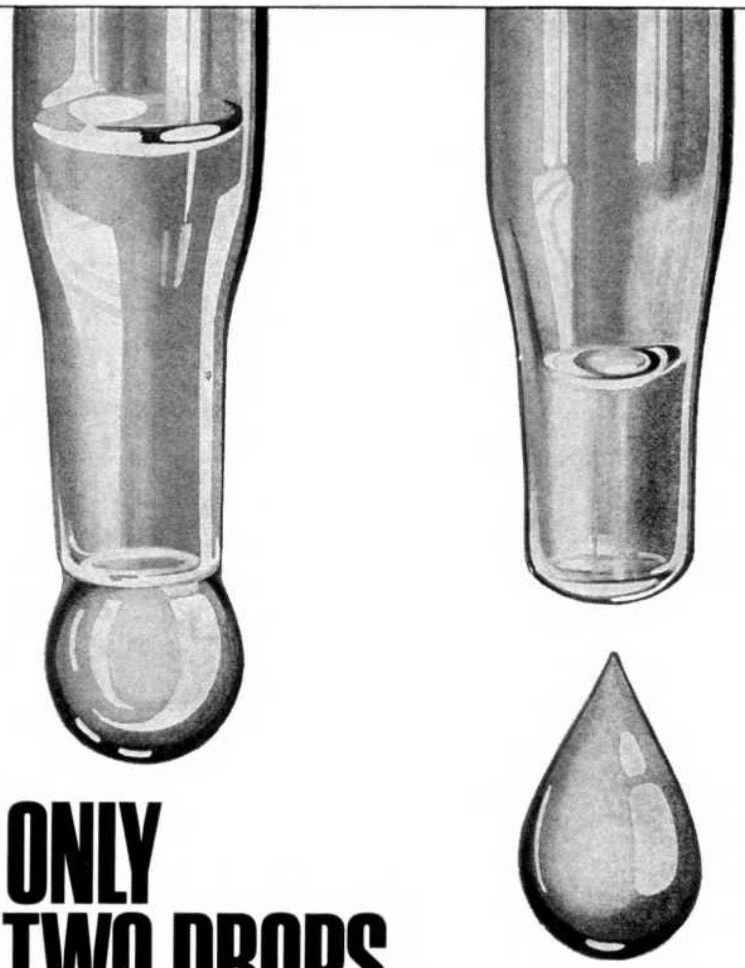

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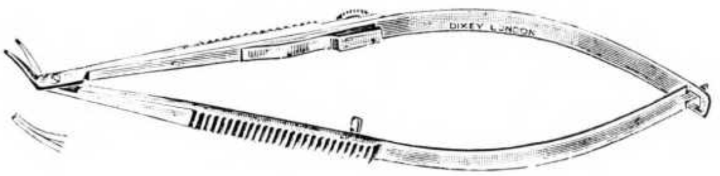

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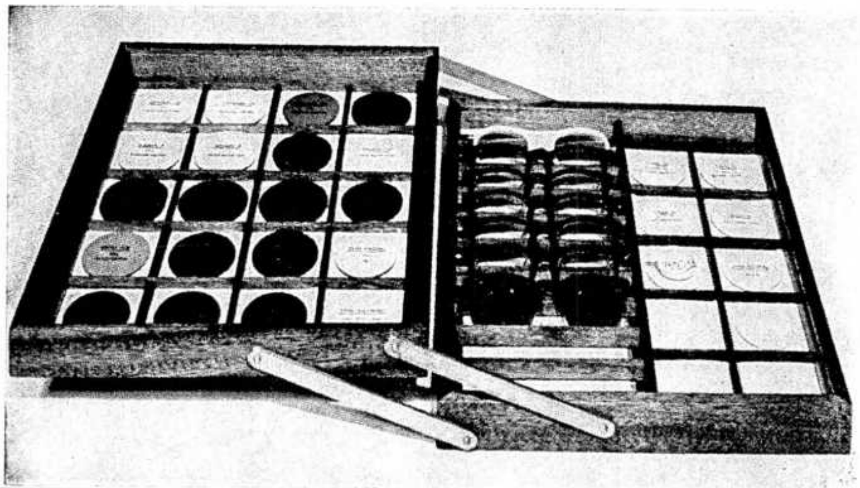

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Editorial: The importance of being collagen

The eye, by its specialized structure and accessibility to examination, provides a unique window for the study of connective tissues when they are involved in systemic disease processes. The severest forms of ocular complications—for example, keratolysis and necrotizing scleritis—underline the vital role which collagen plays in the basic architecture of the eye and emphasize the importance of the study of control mechanisms for its biosynthesis and biodegradation, and their perturbation by pathological processes.

At present the process of extracellular fibre formation is the subject of active investigation. Recent studies (Olsen and Prockop, 1974) have demonstrated the mobilization of previously synthesized procollagen within Golgi vesicles which are then transported to the plasma membrane by the microtubular system. After fusion of the Golgi vesicle with the plasma membrane the procollagen molecules are released into the extracellular space where the non-helical polypeptide extensions are cleaved by a procollagen peptidase. This allows normal fibre bundle formation and cross linking of the molecules to occur (Lapière and Pierard, 1974). Deficient activity of this enzyme is responsible for dermatosparaxis in the calf. In this hereditary disorder of connective tissue, procollagen forms the fibrous framework (Tenaers, Ansay, Nusgens, and Lapière, 1971), and the dermal connective tissue is very fragile (Hanset and Ansay, 1967). Collagen synthesis can also be influenced by the extracellular matrix itself (Nevo and Dorfman, 1972), and this control may be sufficiently sensitive to order the type of collagen synthesized (Slavkin, Croissant, and Guenther, 1975). In developing tissues the distribution patterns of collagen fibre width play an important role in morphogenesis (Robert and Robert, 1975), and in the embryonic eye, physical factors—such as, developing intraocular pressure—may operate to produce the highly structured orthogonal lattice of collagen fibres in the cornea, and so produce a regular conformational response.

The control of collagen biodegradation *in vivo* is less well understood at present, because of the many factors which seem to be involved. Circulating inhibitors of collagenase activity have been reported in serum, an α_2 macroglobulin and α_1 antitrypsin (Eisen, Bloch, and Sakai, 1970), and an α_2 macroglobulin-enzyme complex in synovial fluids from patients with rheumatoid arthritis (Abe and Nagai, 1973). Dissociation of this complex in sodium thiocyanate (NaCNS) results in the 'unmasking' of considerable collagenolytic activity. These circulating inhibitors would therefore seem to be part of the homoeostatic control mechanism to prevent excessive collagenase activity in chronic inflammatory states. In addition, inactive enzyme precursors or procollagenases have been found in the culture media of bone explants *in vitro* (although the possibility that this is an inactive enzyme-inhibitor complex has not been entirely excluded). In these experiments 'unmasking' of the latent collagenase activity was achieved after incubation with a variety of enzymic substances—for example, trypsin, lysosomal extracts, cathepsin B1, Kallikrein, and plasmin (Vaes and Eeckhout, 1975). Many of these substances could well be expected to operate in an inflammatory lesion, although these authors feel that other proactivators may further complicate the system. Collagenase activity may also respond to different controls in various organs. The collagenase production of involuting uterine explants has been shown to be markedly inhibited by progesterone, especially when augmented by dibutyryl cyclic adenosine monophosphate (AMP). Similar inhibitory effects of the cyclic nucleotide and theophylline (a cyclic phosphodiesterase inhibitor) were also found in human skin cultures but progesterone was inactive in this system (Jeffery, Koob, and Eisen, 1975); the same workers also showed that the skin collagenase production was inhibited by extremely low levels of cortisol and dexamethasone which were similarly effective on rheumatoid synovia. The recent demonstration of collagenase activity associated with corneal fibroblasts (Hook, Hook, and Brown, 1973) is obviously of particular interest. When the control mechanisms for this enzyme have been fully studied, the pathogenesis of a suddenly developing keratolysis or scleromalacia perforans will undoubtedly be better understood, and it is not too much to hope that collagenase inhibitors other than corticosteroids will be found, and will prove to be effective in the control of such connective-tissue destruction without concomitantly slowing down the rate of reparative synthesis.

Finally, one must consider how the foregoing outline of the underlying 'mechanics' can be modified by substances derived from the pathological lesions themselves. In this respect the granulomatous lesions of the sclera are of prime importance, as by definition they represent a failure of biodegradation and characteristically are a source of numerous acid hydrolases. In this connexion, ingested inert particles by rabbit synovial fibroblasts have been shown to secrete increased quantities of a collagenase (Werb and Burleigh, 1974) and a neutral proteinase (Werb and Reynolds, 1974). Neutral proteinases are of special importance by their action upon proteoglycan core protein, the dissolution of which enables further enzyme access. The ingestion of antigen/antibody complexes by cells have also been shown to result in the extracellular release of lysosomal hydrolases (Henson, 1971; Weissman, Zurier, Spieler, and Goldstein, 1971). There are thus many other possibilities for collagenase production and/or activation from products secreted by cells involved in the granuloma.

The interrelations between immunopathological stimuli, connective-tissue enzymology and homoeostasis, in the ocular complications of rheumatoid arthritis and other connective-tissue diseases, will undoubtedly provide a very exciting field of ophthalmological investigation in the future.

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Scleritis and episcleritis

PETER G. WATSON* AND SOHAN SINGH HAYREH†
From Moorfields Eye Hospital, City Road, London, and Addenbrooke's Hospital, Cambridge*, and the Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, USA†*

From the earliest available descriptions of episcleritis (Slade, 1838; Rognetta, 1844; Desmarres, 1847) a confusion has existed between scleritis and episcleritis. This has led to contradictory views on the relative severity and prognosis of these conditions, and the erroneous belief that episcleritis is accompanied by serious complications (Viswalingham, 1936; Wood, 1936; Mann and Markson, 1950; Clavel and Teulières, 1958). While Slade (1838), Rognetta (1844), and Desmarres (1847), thought that episcleritis was both common and severe, Mackenzie (1830) considered it to be neither and gave at the same time a vivid and accurate description of scleritis. This confusion still persists today.

In an attempt to clarify the position we have been studying patients with scleritis and episcleritis in a special clinic at Moorfields Eye Hospital during the past 10 years. Of these, 207 patients (301 eyes) with episcleritis and 159 patients (217 eyes) with scleritis were analysed in depth.§ The results reported below have led us to conclude that scleritis and episcleritis are clinically distinct, with a different symptomatology and prognosis and requiring different management.

The incidence of these conditions is not known, but Williamson (1974) suggested that it was about 0·08 per cent of hospital new patient referrals. Our series is from highly selected patients, all being referred from elsewhere, often where there was difficulty in diagnosis, and with unusual problems. This is reflected in the fact that 90 per cent of the patients who had rheumatoid arthritis were seen within a year of the start of the special clinic.

Classification

EPISCLERITIS

Episcleritis has been recognized for over a century, although called by many different names, such as subconjunctivitis by von Graefe (Duke-Elder and Leigh, 1965), subconjunctival phlegma or simple or phlegmatous conjunctivitis by Mackenzie (1830), and episcleritis periodica fugax by Fuchs (1895). Duke-Elder and Leigh (1965) distinguished between nodular episcleritis and rheumatic episcleritis, but such a differentiation appears to be unjustified as rheumatoid arthritis can be associated with either condition. We have classified episcleritis into two types:

1. Simple episcleritis
2. Nodular episcleritis.

SCLERITIS

Many classifications of scleral disease have been proposed (Holthouse, 1893; van der Hoeve, 1934; Franceschetti and Bischler, 1950; Duke-Elder and Leigh, 1965; Sevel, 1967) which have been based on a mixture of clinical and pathological observations. Although we tried to adopt these, from the clinical point of view they have all been unsatisfactory. We eventually adopted the following classification because, although there is some slight overlap between the groups, clinically we have observed several distinct patterns. This classification has proved to be satisfactory and has enabled us to assign almost all the patients to a particular category at the initial examination.

(a) Anterior scleritis
  1. Diffuse scleritis
  2. Nodular scleritis
  3. Necrotizing scleritis
    a. with inflammation
    b. without inflammation (scleromalacia perforans)
(b) Posterior scleritis.

Material

Using the above classification, patients were distributed as in Table I.

Normal anatomy

Before considering the criteria by which the differential diagnosis is reached it is necessary to

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§Mr B. Augier and Mrs B. Phillips of the Institute of Ophthalmology, London, used the University of London computer to analyse the findings

Address for reprints: 22 Parkside, Cambridge, England*, *or* University of Iowa, Iowa City, Iowa 52242, USA†

understand the normal vascular anatomy of the outer coats of the eye. The blood vessels of the episclera are not easily seen in the uninflamed eye, but as soon as the eye becomes congested three quite separate vascular plexuses become readily visible.

1. *Bulbar conjunctival plexus* (Fig. 1)

This is the most superficial plexus of fine hair-like interlacing vessels freely moveable over the underlying structures. Overlying the episclera the conjunctival arteries are derived from two sources—the anterior ciliary arteries at the limbus, and the palpebral branches of the ophthalmic and lacrimal arteries. When they are inflamed the colour is bright red.

2. *Episcleral plexus* (Fig. 1)

The vessels, which are straight and radially arranged, lie in the superficial episclera (parietal layer of Tenon's capsule) at a depth of about one-quarter to one-third of the distance between the surface of the conjunctiva and sclera (Graves, 1937). The visible vessels are mainly veins, accepting the aqueous veins at intervals around the globe. These vessels are moveable over the deep layers, although not so easily as the conjunctival vessels. In the anterior episcleral plexus (anterior to the equator and over the muscle) the vessels belong to the anterior ciliary system; while in the posterior episcleral arterial plexus (posterior to the equator) they are derived from the arteries of the oblique muscles, the posterior ciliary arteries, and the vessels of the optic nerve sheaths (Hayreh and Baines, 1972). When inflamed, these radially arranged vessels can easily be seen, giving the eye a salmon pink colour.

3. *Scleral (deep episcleral) plexus* (Fig. 1)

This plexus consists of a rete (criss-cross) of vessels lying within the visceral layer of Tenon's capsule, closely applied to the sclera. At the limbus the superficial and deep episcleral plexuses merge into one another and terminate in the superficial marginal plexuses of the cornea. When congested this layer looks bluish-red in colour and is immobile.

Clinical examination

Careful examination will determine the depth of the inflammation, so that it is almost always possible to decide when the patient is first seen whether scleritis or episcleritis is present. This depends on accurate observation of the relationship of one layer of vessels to the other and to the underlying sclera.

HISTORY

A detailed clinical history is taken of the patient's ocular and systemic disorders, including family history. Any contact with chemical irritants and solvents is noted, as is any history of allergic conditions, rheumatic, connective-tissue or skin disease, gout, venereal disease, tuberculosis, or sarcoidosis. The site, distribution, and nature of any ocular pain and disturbances of vision are important in deciding the type of inflammation present.

EXAMINATION OF THE EYE

After the visual acuity has been recorded, the following routine of examination is used:

1. *External examination of the eye in daylight*

It is essential to examine a case of episcleritis in daylight as this is often the only way of distin-

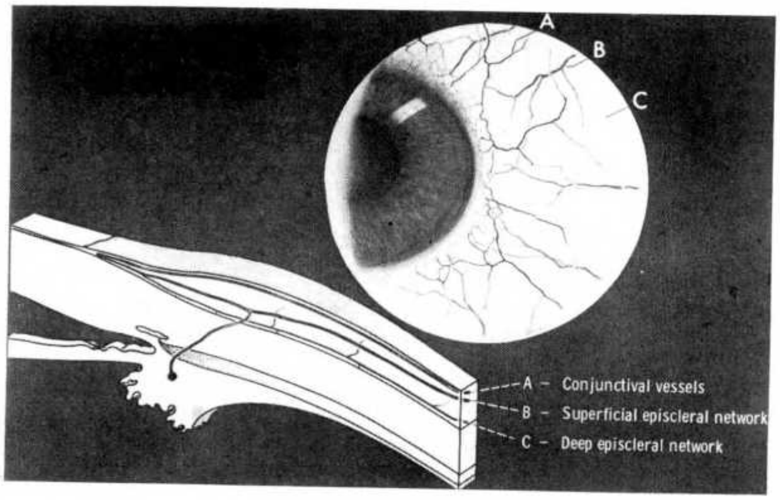
A
B
C
A – Conjunctival vessels
B – Superficial episcleral network
C – Deep episcleral network

FIG. 1 *Normal vascular networks of episclera. There are three layers—the deepest is almost invisible in the uninflamed eye*

guishing episcleritis from the much more serious scleral disease. In episcleritis the colour is salmon pink; in deep scleral disease the colour has a much deeper purple hue. These colour changes are difficult to distinguish in tungsten or fluorescent light. After recurrent attacks of scleral inflammation the sclera may become more transparent and is sometimes thinner, and as a consequence the grey choroid may be seen through the sclera. Sometimes these areas are black and well defined, but more often they give a faint grey tinge to the sclera. This is a particularly important observation in scleromalacia perforans, in which there is no surrounding inflammation. Time and again it is possible to see areas of scleral thinning in daylight which were invisible with the slit-lamp or by illumination with tungsten or fluorescent light.

2. *Slit-lamp microscopic examination*

Of the greatest assistance in distinguishing episcleritis from scleritis is the relationship of one vascular network with another and the changes within them. The object of this examination is to confirm the macroscopic findings. In scleritis, the examination is directed to detecting scleral oedema and the involvement of scleral vessels, ignoring the fact that the overlying episclera will be congested and oedematous. In episcleritis there will be no oedema of the sclera. In addition avascular patches must be diligently searched for, as these indicate a vasculitis and carry a poor prognosis.

Diffuse illumination confirms the macroscopic impression that only episcleral tissue is involved, and in addition reveals any corneal changes.

Slit-lamp examination detects the depth of maximum vascular involvement, infiltration, and oedema of the episclera. Any corneal changes can be categorized and the anterior segment and vitreous scrutinized for evidence of uveitis.

Red-free light examination should never be omitted; it is the ideal method of examining the vascular changes because the vessels become more easily visible. Infiltration of the episclera also shows up as a yellow patch. Adrenaline 1:1000 or 10 per cent phenylephrine can be instilled into the conjunctival sac. This constricts the conjunctival and superficial episcleral vessels more than the deep scleral plexus, thus revealing any underlying scleral disease.

3. *General eye examination*

It is essential to exclude complications such as glaucoma, uveitis, pars planitis, choroiditis, secondary retinal detachment, and optic neuritis. Proptosis and limitation of movement of the extraocular muscles are also looked for as evidence of an involvement of posterior sclera.

SYSTEMIC EXAMINATION

As scleritis is frequently a manifestation, and sometimes the first manifestation, of systemic disease, a thorough physical examination is imperative, special attention being paid to the joints and the cardiovascular system to eliminate a vasculitis.*

Special investigations

ROUTINE STUDIES CARRIED OUT IN ALL PATIENTS

1. *Full blood count*

This included haemoglobin estimation, white blood cell count and differential white cell count, and erythrocyte sedimentation rate.

2. *Rheumatoid arthritis latex agglutination test*

The Rose-Waaler sheep-cell agglutination test was used as a confirmatory test for rheumatoid factor.

3. *Serum uric acid estimation*

4. *Serological tests for syphilis*

A patient who had a positive Wassermann reaction also had the fluorescent treponemal antibody absorption (FTA (ABS)) test, Reiter's complement-fixation test, the Venereal Disease Reference Laboratory (VDRL) test, and the *Treponema pallidum* immobilization (TPI) test to confirm the diagnosis of syphilis. It was recognized that some cases of syphilis might have been missed as only the Wassermann and Kahn tests were performed as a routine. In the case of any abnormal result the test was repeated.

5. *X-rays of the chest and sacro-iliac joints*

These were taken whether the patient had any relevant complaints or not.

ADDITIONAL STUDIES CARRIED OUT IN CERTAIN PATIENTS

1. A full immunological survey for tissue antibodies, soluble immune complexes, complement, lupus erythematosus cells, and antinuclear factor (ANF) were undertaken.
2. Mantoux test.
3. Electroretinograms and electro-oculograms were

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*This was carried out in our clinic by the rheumatologists Dr Fowler, Dr Hazleman, and Dr Lachmann performed initially in all patients but later in the series these were confined to patients with severe disease and to all those with posterior scleritis.

Results

PATIENTS

The data were derived from 207 patients (301 eyes) with scleritis and 159 patients (217 eyes) with episcleritis (Table I).

FAMILY HISTORY

A family history was elicited in 14 patients (four of these patients had simple episcleritis, three nodular episcleritis, six nodular scleritis, and one diffuse anterior scleritis). In the case of the three patients with nodular scleritis the condition was very similar to that seen in close relatives, but in all others the history was indefinite. This indicates that neither episcleritis nor scleritis is a familial condition.

TIME BETWEEN ONSET AND FIRST ATTENDANCE

In contrast to episcleritis, patients with scleritis attended much sooner after the onset of the disease, but even so (presumably because the onset was often insidious) many patients did not seek advice until the pain had become severe, which might not have been for several weeks. Of the patients with episcleritis 13 per cent reported in the first month and 64 per cent within two months. Of those with scleritis the results were very similar, 37 per cent being seen within the first month and 68 per cent before the end of the second month.

Table I *Patients with episcleritis and scleritis whose records were analysed by computer*

Diagnosis	*Patients*	*Eyes*	*Further subdivisions*	*Eyes*	
Episcleritis	159	217	Simple	170	
			Nodular	47	
Scleritis	207	301	Diffuse anterior	119	
			Nodular anterior	134	
			*Necrotizing		
			with inflammation	29	42
			without inflammation	13	
			Posterior	6	

*The incidence of necrotizing anterior scleritis is open to question because, although sometimes obvious when the patient first presents, the disease more often starts as a diffuse or nodular anterior scleritis. Active treatment has certainly prevented some patients from developing necrotic lesions. Only those patients whose diagnosis was absolutely certain have been included in this category

Within one year of the onset of this condition 92 per cent had sought advice.

AGE AND SEX DISTRIBUTION

Scleritis was more than 1½ times as common in women as in men. This contrasted with episcleritis, which was equally common in both sexes.

1. Scleritis

Analysis of the age and sex distribution for the different types of scleritis revealed distinct patterns for each type of scleritis. The diffuse and nodular varieties were most prevalent. In men the peak incidence occurred in the fourth decade ($P = < 0{\cdot}05$); women showed two separate peak incidences, one in the third decade and another in the sixth decade ($P = < 0{\cdot}05$).

Scleritis—diffuse anterior scleritis

In women the disease was commonest in the fourth to seventh decades, with no predilection for any age group. In men it was more prevalent in the third to sixth decades, with a distinct peak during the fourth. The condition was rare in the young and the old.

Scleritis—nodular anterior scleritis

The nodular disease in both sexes was most prevalent from the fourth to sixth decades, but in women there was a very marked peak during the sixth decade.

Scleritis—necrotizing type with inflammation

Of the patients who presented with this severe variety of scleritis the majority were women, but of those who presented during the fourth decade all but one were men.

Scleritis—necrotizing type without inflammation (scleromalacia perforans)

All these patients were women. The age range was 35 to 75 years, most cases occurring in the fifth decade.

Scleritis—posterior scleritis

Posterior scleritis was usually associated with a diffuse anterior scleritis, occurring most frequently in women in their sixth decade, but one woman of 35 years was seen with this condition.

2. Episcleritis

Altogether 88 men and 71 women suffered from episcleritis. There was a significant variation in the sex distribution at different ages. The condition was not seen in childhood. Episcleritis in men occurred maximally from the third to the sixth decade, with a peak in the fourth decade. In women, however, although there was a peak incidence in the fourth and fifth decades, the distribution did not show a predilection for any particular age group. The difference between the peak incidence in the different series was highly significant ($P = < 0.005$). There was no significant difference in the sexes between the time of onset of simple and nodular episcleritis, but nodular episcleritis had a peak incidence in the fifth decade whereas simple episcleritis was most common in the fourth decade ($P = < 0.05$).

INVOLVEMENT OF ONE OR BOTH EYES

1. *Scleritis*

In 45 per cent of the patients the disease was bilateral, but in cases in which the disease involved only one eye, one side was not involved more than the other. When each type of scleritis was further analysed it showed that diffuse anterior scleritis was more often bilateral ($P = < 0.005$) and that nodular anterior scleritis was more often unilateral ($P = < 0.005$). In necrotizing scleritis with inflammation both eyes were more often affected than in patients with scleromalacia perforans. These differences were not, however, significant.

Posterior scleritis was usually unilateral.

In 35 per cent of those patients in whom the condition became bilateral, the other eye was affected between one and three months after the onset of the condition in the first eye. In the rest the disease did not occur in the other eye in less than six years.

2. *Episcleritis*

Of patients with episcleritis, 36·5 per cent developed the condition in both eyes. When only one eye was affected there was no significant difference in the distribution between right and left eyes. Nodular disease occurred more commonly unilaterally than bilaterally. The fellow eye was affected either between one and three months or after six years. There were no exceptions to this in this series.

Symptoms

REDNESS

Almost all patients naturally presented with redness of the eyes. In simple episcleritis the onset was often extremely rapid, the eye becoming flushed within a few minutes of the onset of symptoms; in nodular episcleritis, scleritis, and diffuse anterior scleritis the onset was much more gradual, the intensity of the inflammation increasing over a period of several days. The redness was sectorial, ranging in intensity from the barely noticeable to the fiery red; the degree of inflammation bearing no relationship with the seriousness of the condition. Indeed, in scleromalacia perforans (necrotizing scleritis without surrounding inflammation) there might be no redness of the eye at all.

LACRIMATION, PHOTOPHOBIA, AND CONJUNCTIVAL DISCHARGE

Conjunctival discharge was not a feature of scleritis or episcleritis. Indeed, if the discharge is anything but watery in consistency an incorrect diagnosis has probably been made. Photophobia and lacrimation did not universally accompany episcleritis or scleritis, but where these symptoms were severe they often indicated the presence of a necrotizing process.

In scleritis these complaints were not universal; of the patients with diffuse anterior and nodular scleritis 27 per cent complained of some degree of watering. However, 70 per cent of the patients with necrotizing scleritis complained of photophobia and in 50 per cent the eye watered. Photophobia was unusual in posterior scleritis but about half the patients complained of some lacrimation. No correlation with the presence or type of keratitis could be demonstrated. The incidence of keratitis in each type of scleritis was much less than suggested by the symptoms of photophobia or lacrimation. In episcleritis when these symptoms occurred they were rarely, if ever, severe. Photophobia occurred in 10 per cent of the patients and lacrimation was complained of in 25 per cent. Patients with nodular disease did not have more severe symptoms than those with simple episcleritis. Photophobia and lacrimation showed some correlation with corneal changes, but these symptoms were not always due to changes within the cornea.

PAIN

Scleritis

This is one of the very few severely painful eye conditions and severe pain was complained of in 60 per cent of these patients (Table II). The pain, which was boring in character, was either localized to the eye or generalized, in which case it radiated from the orbital margin to the temple or the jaw in the distribution of the trigeminal nerve. Some patients had been erroneously diagnosed as having migraine or sinusitis, and one patient was thought to have a cerebral tumour. Many other patients

Table II *Types of pain experienced in different types of scleritis (percentage)*

Type of scleritis	*Localized only*	*Generalized only*	*Both localized and generalized*	*Total no. of eyes*
Diffuse anterior	14	15	30	119
Nodular anterior	25	16	20	134
Necrotizing anterior				
With inflammation	0	15	46	29
Without inflammation (scleromalacia perforans)	0	13	19	13
Posterior	0	5	33	6

suffered mild discomfort, but as this did not constitute one of their complaints these patients are not included in the table. Pain is rarely complained of in scleromalacia perforans, in which there is no surrounding inflammation; this is in marked contrast to the pain of necrotizing scleritis, which is the severest of all, often preventing sleep and causing severe loss of weight, and described by Mackenzie (1830) more than 140 years ago

> ['the pain . . . is pulsative and deep seated, the chief pain, however, is not so much in the eyeball, as round the orbit, under the eyebrow, and in the temple, cheek and side of the nose, and is severely aggravated from sunset to sunrise'].

The pain could indeed be so severe that the eye had to be removed.

Episcleritis

Severe pain is not a feature of episcleral involvement. Discomfort, rarely described as pain, occurred in 51 per cent of patients and was almost equally common in simple and nodular types. The sensation in the eye was described as hot, sharp, a slight ache, or irritable. Equally the pain around the eye was described as an ache and, although it sometimes radiated to the temple or jaw, it was never described as boring. However, very occasionally a patient will present with severe swelling of the lids, extreme discomfort, and even miosis and temporary myopia.

The pain or discomfort was localized to the eye in 25 per cent of those patients with simple episcleritis and 33 per cent of those with nodular episcleritis, and was felt around the eye but not in the eye itself in only 9 per cent of those with simple episcleritis and 14 per cent with nodular episcleritis. Both localized and generalized pain was experienced in 19 per cent in simple episcleritis and in 10 per cent in the nodular variety.

Physical signs

SCLERITIS

In the classification of scleritis which we have adopted it has been possible to distinguish each of the various types from their typical clinical appearances although, as already stated, while necrotizing scleral disease sometimes started as a nodular scleritis, its presence could usually be suspected because of the severity of the symptoms.

The essential diagnostic feature in scleritis was the involvement of scleral tissue in the inflammatory process. This usually took the form of scleral oedema which could be detected by observing the outward displacement of the deep vascular network of the episclera (Fig. 2).

Because the episclera was always swollen and congested in scleritis, scleral oedema was the sign which had to be looked for. The deep episcleral vascular plexus was more congested than the superficial network, giving rise to the typical bluish-red colour. The conjunctival vessels were rarely involved.

SCLERITIS—NODULAR ANTERIOR SCLERITIS (Fig. 3)

Although these patients resembled those with nodular episcleritis on cursory examination, detailed examination revealed marked differences and rarely presented any difficulty in diagnosis. The nodule was deep red in colour, totally immobile and quite separate from the overlying congested episcleral tissues. All the vessels were lifted by the nodule. There was, of course, some secondary overlying episcleritis and conjunctival congestion which involved the whole anterior episclera in 20 per cent (Fig. 3). Multiple nodules were seen in 42 per cent, sometimes reaching an enormous size; in 50 per cent they were tender.

SCLERITIS—DIFFUSE ANTERIOR SCLERITIS (Fig. 4)

This was the most benign form of scleritis and it was associated with the least severe of the associated general conditions. The patients might present with an eye in which the sclera was obscured by a diffuse redness and swollen episclera, which might be accompanied in severe cases by conjunctival oedema so severe as to obscure the cornea and protrude from between the eyelids. In these patients adrenaline 1:1000 had to be applied to

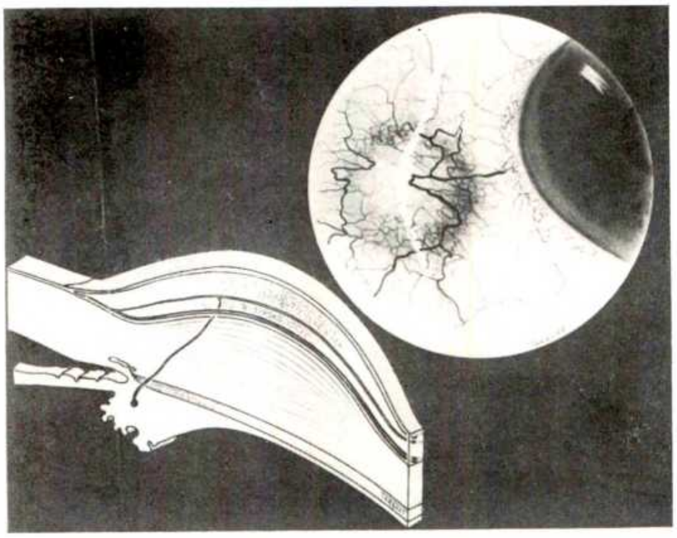

FIG. 2 *Slit-lamp appearances in scleritis. Sclera is swollen so that deep plexus of vessels is displaced forwards. Accompanying episcleritis causes slight separation of superficial networks*

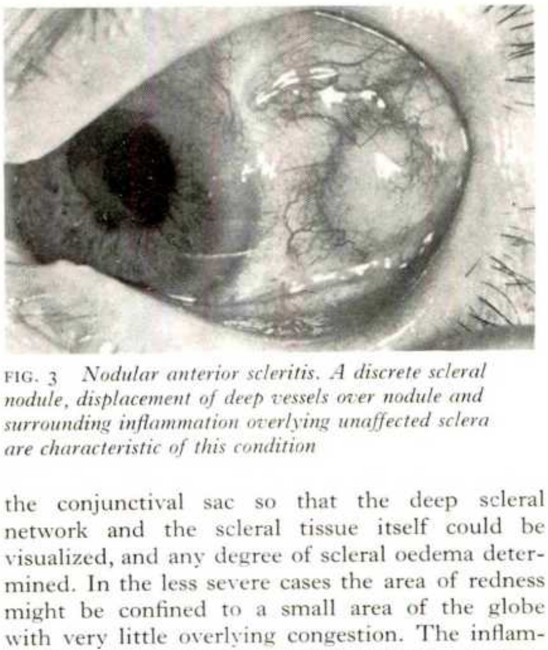

FIG. 3 *Nodular anterior scleritis. A discrete scleral nodule, displacement of deep vessels over nodule and surrounding inflammation overlying unaffected sclera are characteristic of this condition*

the conjunctival sac so that the deep scleral network and the scleral tissue itself could be visualized, and any degree of scleral oedema determined. In the less severe cases the area of redness might be confined to a small area of the globe with very little overlying congestion. The inflammation was more widespread than in the nodular disease, and the extent of the involvement varied from a small area (61 per cent) to the whole anterior segment (39 per cent). The vascular pattern was occasionally grossly distorted and the normal radial pattern lost, with replacement of these vessels with abnormal tortuous new channels (Fig. 5). The eye was tender in 54 per cent of patients.

SCLERITIS—NECROTIZING SCLERITIS WITH SIGNS OF ADJACENT INFLAMMATION (Fig. 6)

This was found to be the most destructive form of the disease. Of these patients 60 per cent developed complications other than scleral thinning and 40 per cent suffered a deterioration of visual acuity. Those patients who were first seen at the onset of the disease presented with a localized patch of scleritis which was associated with acute congestion, sometimes so severe as to merit the term 'brawny' scleritis, but there was nothing in the physical appearances, the aetiology or prognosis, to justify including them as a separate category.

Another physical sign which must alert one to the presence of severe necrotizing scleral disease is the avascularity of a patch of episcleral tissue overlying or adjacent to an area of scleral oedema (Fig. 6). This sign was found in 27·5 per cent of

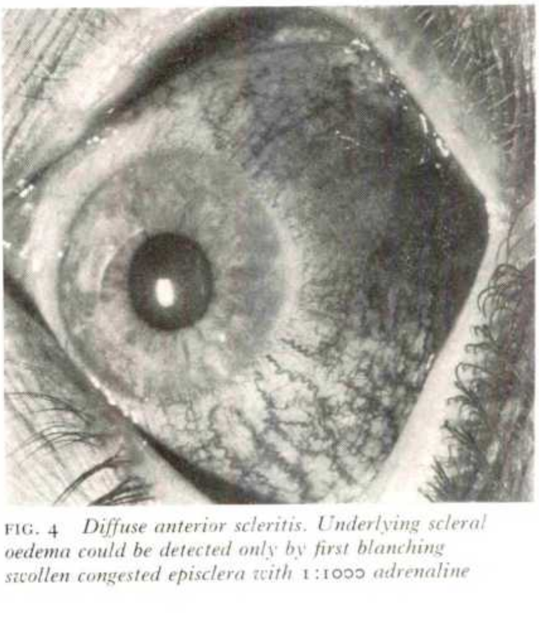

FIG. 4 *Diffuse anterior scleritis. Underlying scleral oedema could be detected only by first blanching swollen congested episclera with* 1:1000 *adrenaline*

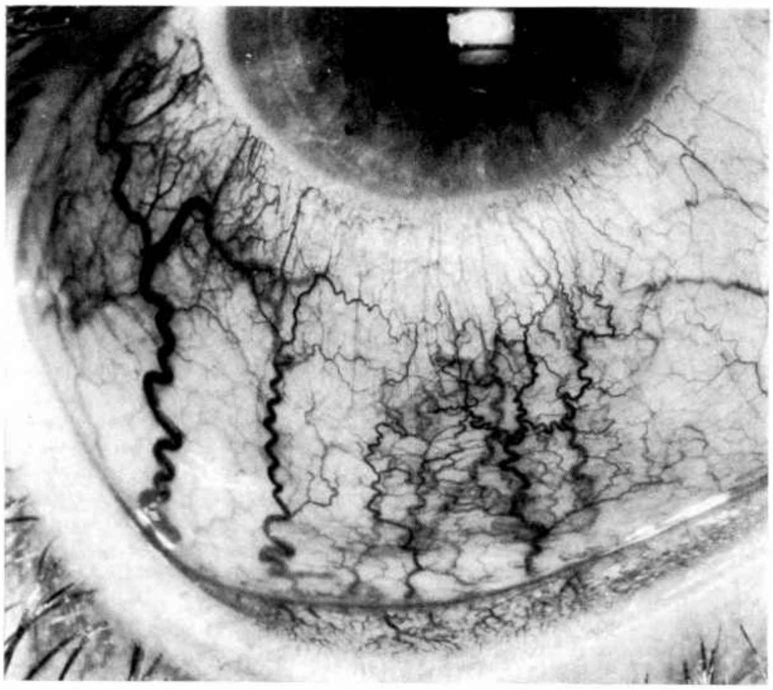

FIG. 5 *Abnormal, tortuous vascular channels which develop after recurrent attacks of diffuse anterior scleritis*

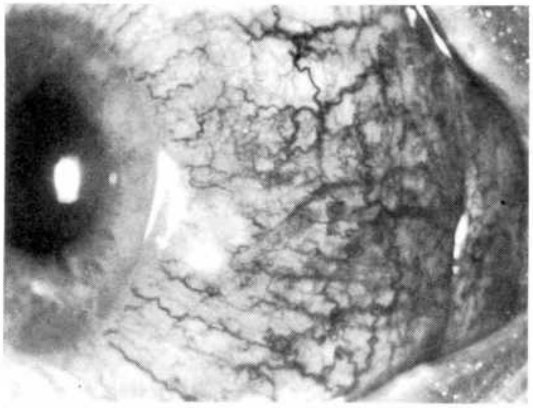

FIG. 6 *Necrotizing anterior scleritis. Superficially this patient appears to be similar to those shown in Figs 4 and 5, but there is an avascular area adjacent to the limbus. If this is not treated, ulceration rapidly occurs similar to that in Fig. 7*

patients with necrotizing scleritis with inflammation and in 23 per cent of those without inflammation (scleromalacia perforans).

Several types of response were noted. In some eyes the inflammation remained localized to one small area, and, if not checked by treatment, resulted in almost total loss of scleral tissue from that area. More frequently the inflammation started in one area and spread in both directions around the globe until the whole of the anterior segment had become involved (Fig. 7). When the inflammation subsided, or was suppressed by treatment, transparent sclera remained. Complications did not supervene until the inflammatory process had progressed through almost 360 degrees. Rarely the whole anterior segment became inflamed at one and the same time, and in some of these eyes areas of necrosis occurred which, if they had not been treated urgently, would have become sequestrated, exposing the underlying uvea. It was not, however, our experience that staphyloma (bulging of the

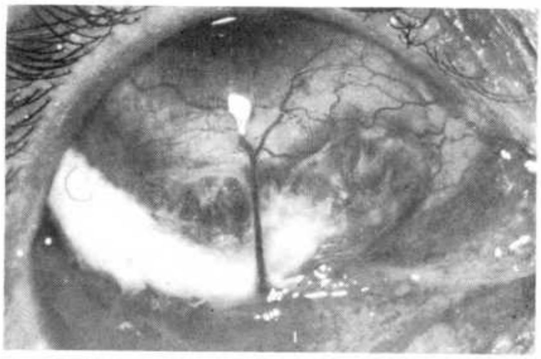

FIG. 7 *Necrotizing anterior scleritis. Late stage of necrotizing scleritis. Inflammation is progressing around the globe, leaving an area of avascular necrotic sclera behind. Almost always these areas are crossed, as here, by a large vein which drains the limbal area on a thin bridge of normal sclera*

uvea into the scleral defect) occurred unless the intraocular pressure became raised above 30 mmHg and had remained high for a prolonged period.

Avascularity of a patch of overlying sclera occurred in 27·5 per cent of the patients. These patches often occurred very early in the disease, and the condition must be treated vigorously if further necrosis is to be prevented. The eye was tender in 40 per cent of these patients.

SCLERITIS—NECROTIZING SCLERITIS WITHOUT ADJACENT INFLAMMATION (SCLEROMALACIA PERFORANS) (Fig. 8)

This condition was associated with long-standing rheumatoid arthritis in 46 per cent of patients. They presented without any subjective symptoms, the doctor or the patient having noticed either a greyish or yellowish patch on the sclera or, in more severe cases, areas of complete loss of tissue. Any inflammatory change was minimal. There was no reactive oedema because it appeared that the episcleral tissue overlying the defect had disappeared, and elsewhere it was so thin as to be almost invisible. The number of vessels in the remaining episcleral tissue also appeared to be much diminished, giving a porcelain-like appearance to the white of the eye when viewed from a distance. Altogether 40 per cent of the patients had more than one necrotic patch. We had the opportunity of watching some of these develop and the pattern seemed to be the same. The conjunctiva and remaining episclera might become suffused over a wide area or might remain unaltered. A demarcation line would develop in the sclera, like a circular crack, and the area inside this would take on a yellowish or greyish appearance and after a variable period would separate as a sequestrum together with the overlying episclera. Large abnormal vessels surrounded and crossed the area, and where they crossed it near the limbus they left an area of about 0·5 mm on either side of a relatively normal sclera. The resulting defect was covered by a very thin layer of connective tissue which appeared to be derived from the conjunctiva. Unless the intraocular pressure rose, no staphyloma was seen. In no case was the eye tender to the touch.

SCLERITIS—POSTERIOR SCLERITIS

We were certain of the diagnosis in six cases (2·9 per cent), but it was suspected in several cases, and it was likely that others escaped our notice. Since there are no apparent external signs of posterior scleritis unless there is also an associated anterior scleritis, the presence of proptosis, exudative detachment and other fundus changes, including papilloedema, may mislead the ophthalmologist to such an extent that the correct diagnosis is never made. In view of this it is possible that the incidence of posterior scleritis may not be as low as indicated by the present series, as our patients were all referred from elsewhere. The condition was unilateral in four of the six cases.

PRESENTING FEATURES IN POSTERIOR SCLERITIS

Symptoms. In all the patients there was extreme pain and tenderness.

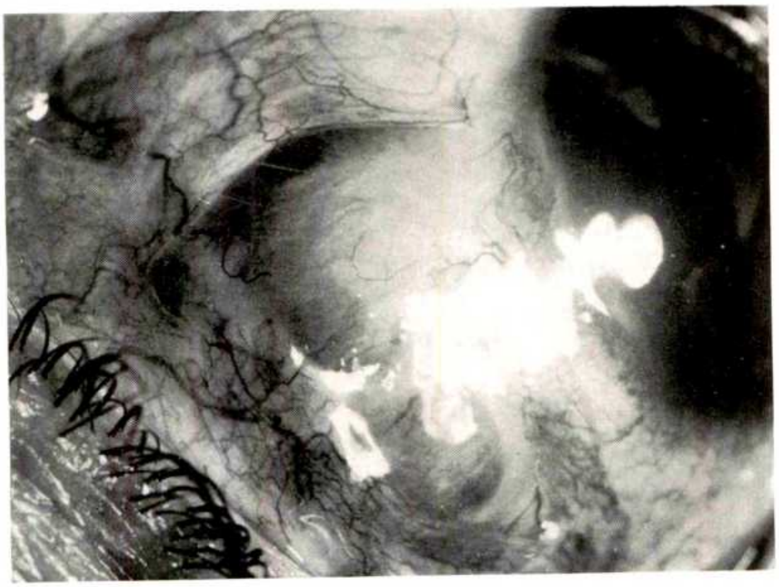

FIG. 8 *Necrotizing scleritis without inflammation (scleromalacia perforans). Almost complete dissolution of scleral collagen occurring with little if any surrounding inflammation in woman of 60 years with long-standing rheumatoid arthritis*

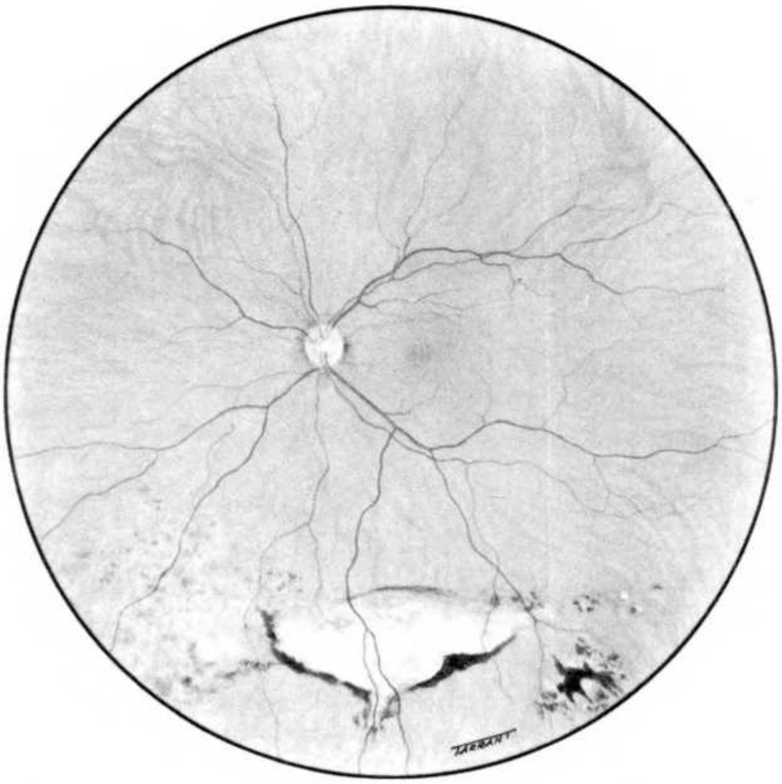

FIG. 9 *Appearance of fundus after resolution of extensive serous detachment in patient with posterior scleritis who presented with diminution of vision, anterior scleritis, slight proptosis, and a diffuse leak early in dye transit on fluorescein angiography*

Visual acuity. All eyes except one showed some reduction in visual acuity.

Fundus changes. In four of these patients there was an exudative retinal detachment associated with swelling of the optic disc and an anterior diffuse scleritis. The anterior scleral involvement was minimal and had to be looked for carefully, but the retinal changes were typical. Areas of exudation occurred beneath the retina, giving the appearance of pale greyish-white spots with a surrounding dark greyish line that could be seen through the overlying serous detachment (Fig. 9). In the early stages there was a diffuse leak early in the dye transit on fluorescein angiography.

Proptosis. Two patients presented with proptosis, a diffuse anterior scleritis, limitation of ocular movements, especially upwards, and retraction of the lower lid (Fig. 10) when attempting to look upwards. This physical sign seemed to be specific for this condition and was presumably caused by infiltration of both the tendons and the muscle cone in the region of the posterior scleritis. Diplopia was also a presenting feature of posterior scleritis because of involvement of the muscles and tissues

FIG. 10 *Posterior scleritis. Retraction of left lower lid in patient with posterior scleritis who also had severe limitation of ocular movements. Ocular movements became normal with treatment but the lid sign remained*

within the muscle cone by the inflammatory process. All these features returned to normal after treatment. The exudative detachment in one patient disappeared within five hours of starting treatment. The site of inflammation remained pale and white after the inflammation had disappeared, leaving some areas of pigment migration at the edges, giving the appearance of a high-water mark.

EPISCLERITIS

Simple and nodular episcleritis differed in their clinical signs, but in both, the oedema or infiltration were entirely within the episcleral tissue; the sclera itself was not involved. The episcleral vascular network was maximally congested, with some congestion of the conjunctival vessels and minimal congestion of the scleral vessels (Fig. 11).

EPISCLERITIS—SIMPLE EPISCLERITIS

The redness of the episclera was often very intense and was localized to one sector in 69 per cent of patients and generalized in 31 per cent. The episcleral vessels, although engorged, retained their normal radial position and architecture. The colour varied from fiery red to a mild red flush but did not have the bluish hue so typically seen in scleritis.

In simple episcleritis there was a diffuse oedema of the episcleral tissue which was sometimes infiltrated by greyish deposits which appeared yellowish in red-free light. The depth of the oedema and its effect on the vascular plexus was best recognized by slit-lamp examination, using a narrow beam. The eye was tender to the touch in 33 per cent of cases.

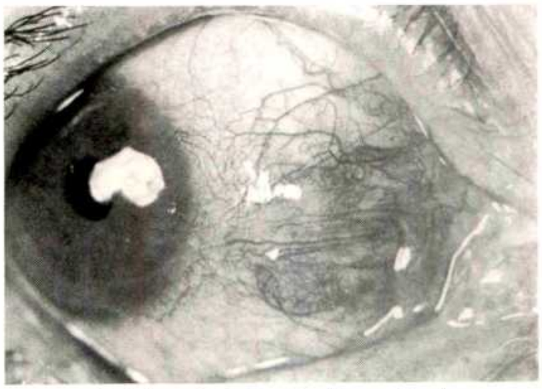

FIG. 12 *Nodular episcleritis. Swelling and oedema confined to episcleral tissue and vessels retain their normal architecture*

EPISCLERITIS—NODULAR EPISCLERITIS

In contrast with simple episcleritis the oedema and infiltration of nodular episcleritis were localized to one part of the globe, except in seven eyes in which the redness was widespread. A nodule from within the episcleral tissue, which was surrounded by some congestion, was mobile on the underlying sclera and there was no involvement of the sclera in the oedema. The scleral plexus of vessels could be distinguished deep to the nodule lying flat on the sclera, which retained its normal contour (Figs 11 and 12). The nodules were usually single but were sometimes multiple, reaching the size of a large pea. The eye was tender to the touch in 40 per cent.

Vascular changes in the episclera

Although vascular changes were most unusual in episcleritis, vessels that appeared to be abnormal

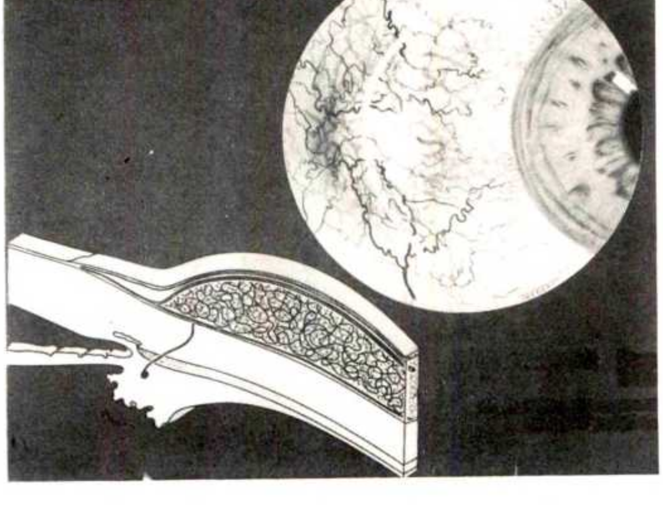

FIG. 11 *Episcleritis. Although deep vascular network is congested there is no scleral swelling, oedema and infiltration being confined to episclera*

either in course or type were noted in 19 eyes with simple episcleritis and 10 eyes with nodular episcleritis. All these patients had had recurrent attacks at the same site for many years. One patient showed avascularity of the episcleral nodule which was thought to be due to the intensity of the oedema, as the vessels returned to normal as soon as treatment was given.

Complications

Complications of some sort were found in only 15 per cent of patients with episcleritis but ocular complications, other than simple increased scleral transparency or thinning, occurred in 57 per cent of all patients with scleritis. The complications looked for and analysed were:

1. Fall in visual acuity
2. Keratitis
3. Cataract
4. Uveitis
5. Glaucoma
6. Scleral thinning (and scleral defects)

Fall in visual acuity

SCLERITIS

A total of 42 eyes (14 per cent) in patients with scleritis lost a significant amount of vision after the disease had been present for one year. This fall in visual acuity was attributed to cataract (five eyes), anterior uveitis (two eyes), and posterior uveitis (two eyes). The commonest reason for the fall in visual acuity was the association with keratitis (Table IV), particularly if this was accompanied by a uveitis.

EPISCLERITIS

No patient with episcleritis had a fall in visual acuity during the period of follow-up.

Table III *Fall of visual acuity in scleritis*

Type of scleritis	*Total no. of eyes*	*Fall in visual acuity 2 lines or more during period of follow-up (per cent)*
Diffuse anterior	119	15
Nodular anterior	134	7
Necrotizing anterior		
With inflammation	29	27
Without inflammation (scleromalacia perforans)	13	31
Posterior	6	50

Table IV *Fall of visual acuity in scleritis due to keratitis*

Keratitis	*No. of eyes with fall in visual acuity during follow-up*
Superficial	2
Midstromal	3
Deep	0
Guttering	3
Others	5

Keratitis

SCLERITIS

Corneal changes of a type characteristically seen in scleritis were observed in 29 per cent of patients. This keratitis can be serious, leading to permanent changes in the cornea; these are so characteristic that when certain types of sclerosing keratitis and lipid changes are seen in an eye which is otherwise normal, it can be inferred that the patient has had scleritis at some time in the past.

Characteristic corneal changes were seen in each type of anterior scleritis and could be classified as follows:

Nodular scleritis

- i. Localized stromal keratitis
- ii. Localized sclerosing keratitis

Diffuse scleritis

- i. Acute stromal keratitis
- ii. Sclerosing keratitis
- iii. Corneal guttering

Necrotizing scleritis

- i. Sclerosing keratitis
- ii. Keratolysis

The incidence of keratitis in different types of scleritis is given in Table V.

Acute stromal keratitis (Fig. 13)

In the severe necrotizing scleritis of acute onset the cornea became oedematous and dense white infiltrates appeared within the stroma (Fig. 13). These were sometimes central and sometimes peripheral and might coalesce as the disease progressed. If, in addition, there was anterior chamber activity, keratic precipitates adhered to the posterior corneal surface. The opacity was sometimes surrounded by a 'precipitin' ring. If the scleritis was treated vigorously with full doses of steroids

Table V *Keratitis and vascularization of the cornea in scleritis*

Type of scleritis	*Total no. of eyes*	*Keratitis*					*Corneal vascularization*			
		Superficial	*Mid-stromal*	*Deep*	*Guttering*	*Other*	*Superficial*	*Mid-stromal*	*Deep*	*Other*
Diffuse anterior	119	8	10	2	4	4	3	2	3	2
Nodular anterior	134	6	14	4	5	6	5	0	1	0
Necrotizing anterior										
With inflammation	29	4	4	2	4	3	2	1	3	0
Without inflammation (scleromalacia perforans)	13	0	3	1	3	0	1	3	2	1
Posterior	6	0	0	1	0	0	0	0	0	0
Total	301	18	31	10	16	13	11	6	9	3

these opacities could disappear without trace. More usually, however, linear opacities within the stroma remained and, if central, these impaired vision.

Sclerosing keratitis (Fig. 14)

The corneal opacities associated with scleral disease usually appeared less dramatically; the cornea adjacent to the swollen sclera became oedematous and vessels grew into this oedematous area. Vascularization never seemed to precede the oedema. Although these opacities usually occurred close to the limbus they could appear in the superficial and midstroma centrally in the cornea, having no obvious connexion with the site of the scleral disease.

Whatever the type or site of the corneal lesion, treatment of the scleritis brought about resolution of the keratitis which might be complete or, more usually, the lamellae of the cornea were altered to leave thin linear opacities which looked exactly like the sugar crystals of 'candy floss' (Fig. 14). Crystalline (candy-floss) opacities were seen in 23 patients with diffuse and another 23 patients with nodular scleritis, and five patients with necrotizing scleral disease. This type of corneal change could not be correlated with vascularization or any particular aetiological agent. Keratolysis was observed in four patients, all of whom had severe necrotizing anterior scleritis. These opacities, once formed, never disappear. In very severe cases the opacification of the cornea progressed circumferentially until only a central clear area in the cornea remained, and even this area might disappear, resulting in a 'scleralized cornea'. Corneal grafting was very successful in restoring the visual acuity in these patients.

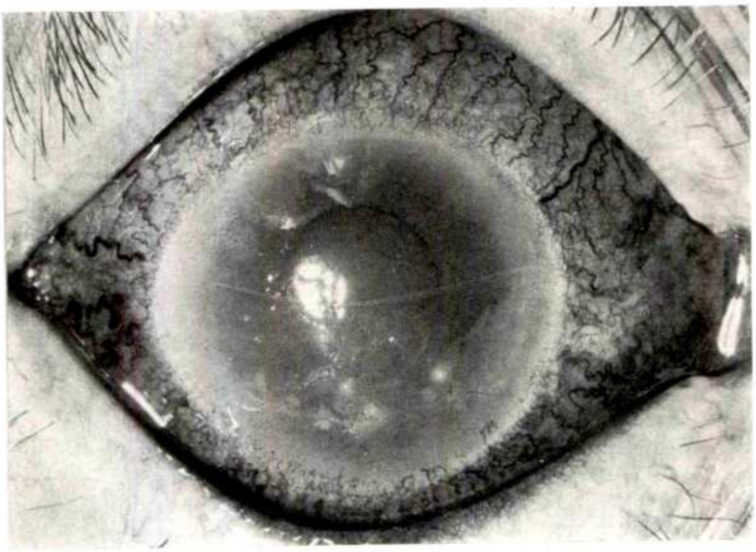

FIG. 13 *Acute stromal keratitis in scleritis. Dense white infiltration in cornea in same patient as in Fig. 9. Immune rings similar to those seen in Fig. 14 appeared round these lesions. All corneal signs, etc. disappeared after treatment*

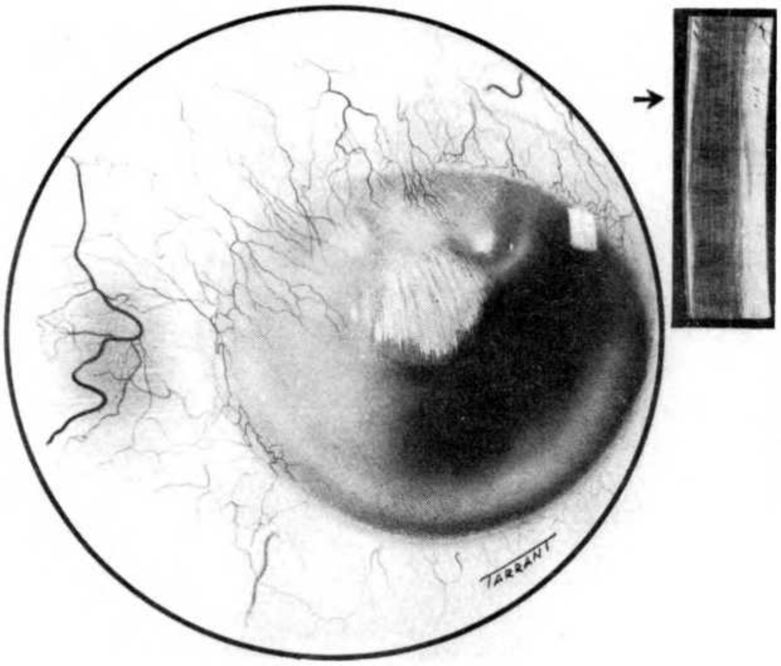

FIG. 14 *Sclerosing keratitis in scleritis. A 66-year-old woman with a 13-year history of recurrent bilateral diffuse sclero-keratitis with crystalline (candy-floss) deposits in the deep stroma and a 'precipitin ring' around the infiltration at 12.0 o'clock. The vascularization is passive. Vessels enter the cornea only at site of advancing edge of corneal change and at late stage in disease. Acute stromal keratitis will progress to this if left untreated*

Limbal guttering

Guttering of the peripheral cornea was not infrequently seen, particularly in patients who had severe long-standing rheumatoid arthritis. These gutters never extend more than 2 mm from the limbus, but may become circumferential and very thin, requiring grafting. Erosion of the deep stroma resembling Terrien's disease may also occur, and in one case this led to an expansion of the eye to 18 dioptres of astigmatism in that axis, necessitating corneo-scleral grafting over the affected region (Fig. 15).

Keratolysis

The most severe corneal disease of all is keratolysis. This was seen in only four patients, all of whom had very severe necrotizing scleritis, usually, but not invariably, accompanied by loss of scleral tissue. In this terrifying situation the whole stroma of the cornea disappeared with alarming rapidity (Fig. 16). The progress could have been stopped by full steroid therapy but only after very prolonged treatment would any corneal tissue have been re-formed. It was usual therefore to graft these eyes when the scleritis had become well controlled or if rupture appeared imminent.

Lipid deposition occurred in areas where the cornea had been damaged and at the inner edge of a long-standing corneal gutter. This was presumably because of interference with the usual flow of these metabolites to the limbus and it was not a product of the corneal inflammation.

Posterior corneal changes

Although we have not analysed this series for it, we have recently come to recognize another pattern of corneal change in scleritis (Holt-Wilson and Watson, 1974), which presented as an interstitial keratitis indistinguishable from that seen in congenital syphilis but which occurred in patients who had a mild scleritis and in whom the serological investigations were entirely negative (Fig. 17).

Keratitis could be considered the sole reason for a severe fall in visual acuity in 13 eyes (4 per cent).

EPISCLERITIS

Minimal corneal changes were seen in 15 per cent of the patients with simple episcleritis and in 15 per cent of those with nodular disease, but these were never severe. The oedema of the cornea occurred when the episcleral inflammation was close to the limbus and seemed to be a consequence of this adjacent inflammation. Keratitis was most common in the superficial and midstromal layers of the cornea in both varieties. Some localized corneal guttering occurred in six eyes after recurrent attacks in the same area for many months. Vascularization of the cornea occurred in six eyes, the vessels being deep in three, midstromal in one,

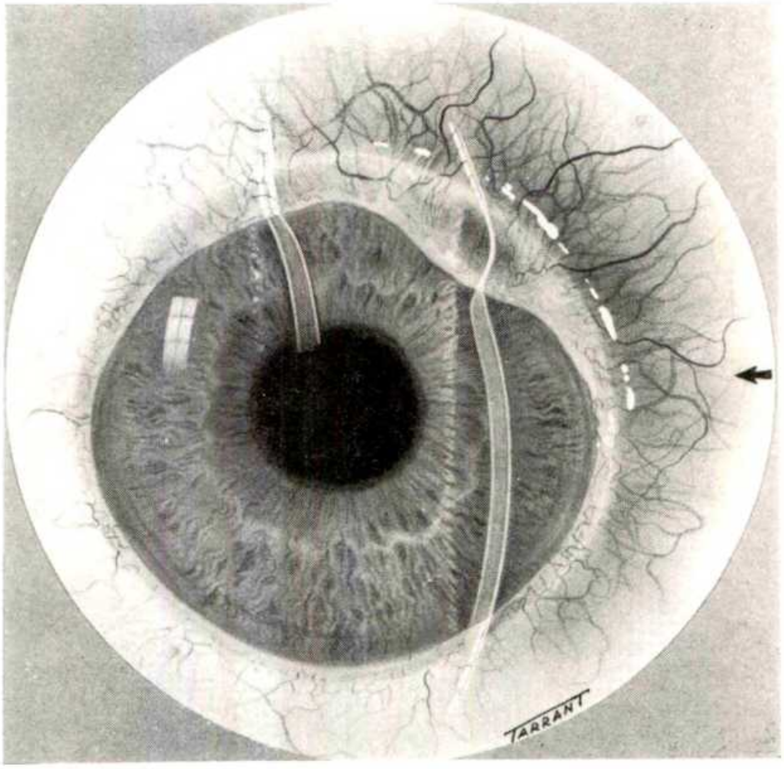

FIG. 15 *Limbal guttering in scleritis. A 24-year-old man with a 10-year history of unilateral scleritis localized to area of sclera between 12.0 and 2.0 o'clock. Cornea in area has become guttered and produced a 'Terrien'-like change. This area required grafting (Fig. 19) because of rapidly increasing expansion of globe in this axis*

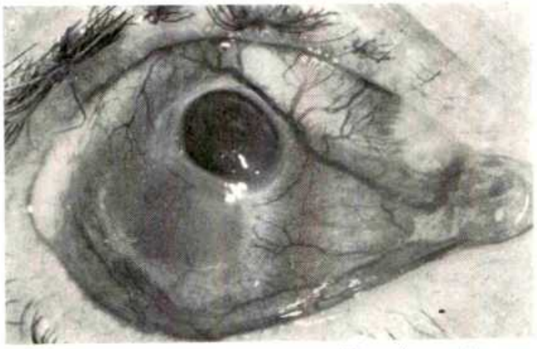

FIG. 16 *Keratolysis. Severe necrotizing changes in both cornea and sclera which occurred in a period of five weeks in a 74-year-old woman. Systemic steroids suppressed inflammation and both cornea and sclera were grafted successfully*

and superficial in two. No serious complications were found in any of the patients studied.

Cataract

SCLERITIS

Cataracts were detected in only 22 eyes, 7 per cent. These were bilateral and senile in type in 15 eyes. In 12 eyes the cataract was noted to have become worse during the course of the disease. All these patients were between the ages of 55 and 80 years and all had serious scleral disease. In only three patients (five eyes) with an associated long-standing anterior uveitis was it felt certain that the sclero-uveitis was responsible for the cataracts. In two of these patients it was particularly noticeable that the cataract had developed rapidly once the scleritis had involved the sclera through 360°. Three of these cataracts have required extraction. The sclero-corneal wound has healed normally after cataract extraction in spite of continuing active scleritis in the area of the wound. One eye developed a steroid-induced cataract after

Table VI *Keratitis in episcleritis*

Episcleritis	*Type of keratitis*			
	Superficial	*Mid-stromal*	*Deep*	*Guttering*
Simple	7	14	3	5
Nodular	2	4	1	1
Corneal vascularization	2	1	3	0

NB Some eyes showed more than one type of keratitis

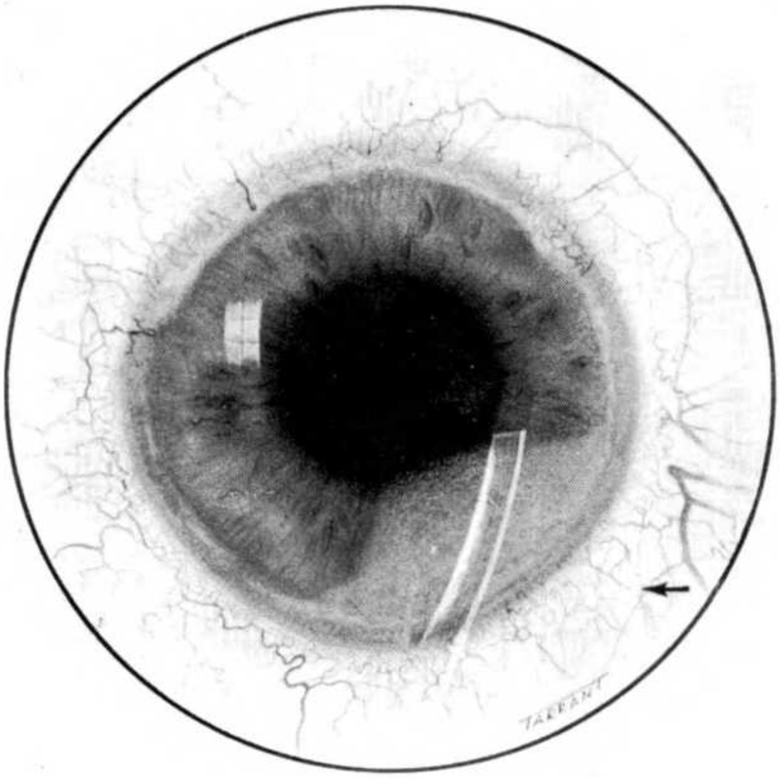

FIG. 17 *Deep stromal corneal changes as seen in group of young patients with diffuse anterior scleritis. When vessels enter cornea they do so adjacent to Descemet's membrane, giving the appearance of a syphilitic interstitial keratitis*

prolonged local steroid treatment. Five eyes in which cataract developed also showed a severe long-standing anterior uveitis.

EPISCLERITIS

Eight patients, six of whom were over 60 years old, were found to have cataracts. However, in none of these patients did the cataract progress during the period of follow-up, nor were the cataracts worse in the eyes with episcleritis. One patient had developed a typical steroid cataract from prolonged local steroid treatment before we saw him. No correlation was found between episcleritis, uveitis, or cataract.

Uveitis

SCLERITIS

Anterior uveitis

There was evidence of anterior uveitis in 30 per cent of all the eyes with scleritis. It was found universally in those patients with scleromalacia perforans (Table VII). However, it did not always occur in those with necrotizing scleritis, nor was there any particular correlation between the presence of an anterior uveitis with any particular disease. When an anterior uveitis did occur it tended to be long-standing and intractable.

The distribution was evenly divided between unilaterally and bilaterally affected eyes. Only two patients developed a uveitis in the other, apparently unaffected, eye.

Posterior uveitis

All the patients with posterior scleritis had posterior uveitis, but posterior uveitis was also found in those who had an anterior scleritis (Table VIII).

In two of the patients with nodular anterior scleritis, and in three of those with necrotizing disease, discrete areas of subretinal exudation

Table VII *Anterior uveitis in scleritis*

Type of scleritis	*Eyes*	*Anterior uveitis (per cent)*
Anterior		
Diffuse	119	35
Nodular	134	17
Necrotizing	29	37
Scleromalacia perforans	13	100
Posterior	6	66

Table VIII *Posterior uveitis in scleritis*

Type of scleritis	*Eyes*	*Posterior uveitis (per cent)*
Anterior		
Diffuse	119	13
Nodular	134	3
Necrotizing	29	17
Scleromalacia perforans	13	23
Posterior	6	100

could be seen at the periphery of the fundus with a 'high-water mark' of retinal and subretinal oedema around the patches of exudation. One patient developed an annular choroidal detachment at the height of the scleritis.

EPISCLERITIS

No severe uveitis occurred in this series. Mild uveitis, detectable on the slit-lamp by an increase in the number of cells in the anterior chamber and a mild aqueous flare, was found in 12 eyes. In two unilateral cases, flare and cells were noted in the unaffected eye. No correlation between corneal involvement and uveitis was detected.

Glaucoma

SCLERITIS

Glaucoma was present in 35 eyes (11·6 per cent), of which 20 per cent showed associated keratitis.

Of the patients with secondary glaucoma nine had no abnormality other than scleritis, seven also had keratitis, and six uveitis.

Secondary glaucoma often accompanies severe anterior scleritis, the cause apparently being due to obstruction of the outflow channels by oedema because the intraocular pressure falls and the outflow of aqueous rises as soon as the scleritis comes under control with systemic treatment. Six patients, who had anterior synechiae and a long-standing uveitis with secondary glaucoma, required other medication for control of the intraocular pressure. None of these patients has yet required surgery.

No patient with posterior scleritis had glaucoma. One patient developed a steroid glaucoma which has required continuous medication for its control.

EPISCLERITIS

Glaucoma was detected in nine eyes (4 per cent). Two patients were known to have chronic open-angle glaucoma before the onset of the episcleritis. Five eyes had developed a steroid glaucoma from prolonged administration of local steroids. In no instance could the glaucoma be attributed to the episcleral inflammation, although there was corneal involvement in one eye.

Scleral thinning

When the sclera looked blue in the daylight when contrasted with surrounding white sclera this was regarded in our analysis as scleral thinning. The sclera in many of these patients had become transparent rather than thin; however, the blue patch appeared only in cases in which there had been active disease. The change in transparency was usually not apparent during the active stage of the disease but it was observed at the site of recurrent simple or nodular episcleritis in 19 eyes (8 per cent), and in 36·5 per cent of eyes affected with scleritis, during the period of follow-up.

After repeated attacks of episcleritis, particularly if these occurred at the same site, the sclera might become transparent but not thin. Similarly in diffuse and nodular scleritis the sclera might become transparent with the blue choroid showing through. This was easily seen in daylight and could be used as an indication of previous scleral inflammation. Ectasia and destruction of scleral tissue occurred only in necrotizing scleritis. This could take the form of an avascular area appearing in the centre of an area of scleritis, which then broke down to form a slough and eventually to leave an area of thinning.

Table IX *Glaucoma in scleritis*

Type of scleritis	*Total*	*Total with glaucoma*	*Primary open-angle*	*Primary closed-angle*	*Secondary*	*Steroid-induced*
Diffuse anterior	119	12	6	0	6	0
Nodular anterior	134	11	6	0	5	0
Necrotizing anterior	29	8	2	0	5	1
Scleromalacia perforans	13	4	0	0	4	0
Posterior	6	0	0	0	0	0
	301	35	14	0	20	1

Table X *Scleral thinning or transparency in scleritis*

Type of inflammation	*Total no. of eyes*	*Eyes with thinning*		*Total incidence (per cent)*
		Localized	*Generalized*	
Episcleritis				
Simple	170	12	3	9
Nodular	47	4	0	9
Scleritis				
Diffuse anterior	119	23	15	32
Nodular anterior	134	35	2	28
Necrotizing anterior	29	11	10	69
Scleromalacia perforans	13	7	6	100
Posterior	6	1	0	16

In the type of necrotizing scleritis which progressed around the globe, the area behind the advancing edge could become extremely thin, and sometimes melted away altogether. In the variety of necrotizing scleritis without inflammation (scleromalacia perforans), the episclera was usually extremely thin (Fig. 8), and the underlying sclera would become white, develop a demarcated margin, and then become sequestrated. The conjunctiva and thin episclera overlying this process might be slightly congested but this was by no means always the case. A combination of A- and B-scan ultrasound could be used to distinguish between thinning and increased transparency—A-scan being used to estimate the thickness and B to locate the lesion.

Scleral defects (Fig. 18)

Scleral defects, as opposed to scleral thinning or increased scleral transparency, were seen only in the severest forms of necrotizing disease. When the necrotizing disease was associated with inflammation, the episclera became avascular, overlying the area which would eventually become sequestrated. Treatment at this stage would prevent sequestration. In scleromalacia perforans sequestration might take place without any warning. The loss of tissue in either condition might involve only a part of the scleral thickness.

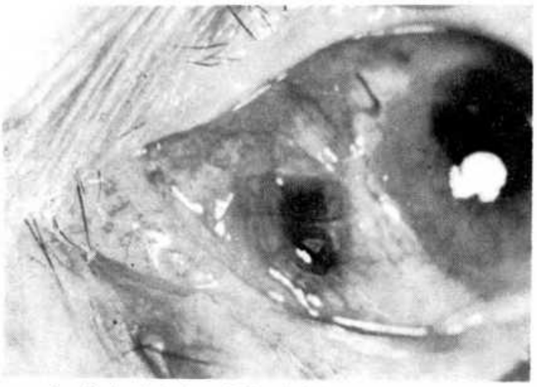

FIG. 18 *Scleral defect. Scleral defect occurring in patient with severe necrotizing scleritis. Ciliary body is exposed but no staphyloma occurs unless intraocular pressure rises above* 40 *mmHg*

Sequestration occurred in 22 eyes (7 per cent). Loss of tissue took place in 41 per cent of eyes with necrotizing disease associated with inflammation, and in 77 per cent of those without inflammation. The rest of these eyes developed severe thinning without sequestration. Of eyes with scleral defects 59 per cent also had keratitis, although this was accompanied by a loss of corneal tissue (keratolysis) in only three eyes (Fig. 16). No scleral defects developed in patients who had episcleritis or any of the less severe forms of scleritis.

Associated systemic diseases

The incidence of the various systemic conditions detected in this series is summarized in Table XI.

In eyes where scleritis and episcleritis coexisted, the area of severe damage occurred where the sclera was involved, and not where the episclera was inflamed without deep involvement.

We have observed, however, that the patients with herpes zoster ophthalmicus developed an episcleritis at the time of the vesicular eruption. The episcleritis disappeared as the skin condition subsided. Three patients developed a severe nodular scleritis two or three months later at the site of the original lesion. This does not imply that the episcleritis progressed to the scleritis, because there was a distinct interval between the two episodes during which the eye was apparently normal. Since making this observation we have studied a further 20 patients who were not included in this series presenting with herpes zoster ophthal-

Table XI *Incidence of associated systemic diseases in episcleritis and scleritis*

Disease	*Episcleritis*		*Scleritis*				
	Simple	*Nodular*	*Diffuse anterior*	*Nodular anterior*	*Necrotizing anterior*	*Scleromalacia perforans*	*Posterior*
Rheumatoid arthritis	5	2	8	4	3	6	0
Ankylosing spondylitis	0	0	1	0	0	0	0
Psoriatic arthritis	0	0	0	3	0	0	0
Systemic lupus erythematosus	0	0	0	1	1	0	0
Periarteritis nodosa	0	0	0	0	2	0	0
Systemic vasculitis	0	0	1	0	1	0	0
Wegener's granulomatosis	0	0	0	0	1	0	0
Relapsing polychondritis	0	0	0	0	2	0	0
Rheumatic heart disease	2	1	1	1	0	0	0
Palindromic rheumatoid	0	0	0	0	2	0	0
Associated with hypersensitivity disorders							
Erythema nodosum	0	0	0	2	0	0	0
Severe asthma or hay fever	0	0	2	0	0	0	0
Erythema multiforme	1	0	0	0	0	0	0
Henoch-Schönlein purpura	1	0	0	0	0	0	0
Penicillin sensitivity	2	0	0	0	0	0	0
Contact dermatitis	2	1	0	0	0	0	0
After desensitization vaccination	2	0	0	0	0	0	0
Rosacea	1	2	0	2	0	0	0
Associated with granulomatous conditions							
Tuberculosis							
Active	1	0	1	0	3	0	0
Inactive	1	2	0	0	0	0	0
Syphilis	0	1	1	3	2	0	0
Associated with virus infection							
Herpes zoster	2	1	2	14	0	0	0
Herpes simplex	0	0	0	2	0	0	0
Associated with metabolic disorders							
Gout	6	5	2	3	0	0	0
Other associated conditions*	1	0	10	7	1	0	0

*In simple episcleritis one patient had regional ileitis
In diffuse anterior scleritis 10 patients had other diseases—orbital granuloma (1), essential hypertension (3), postirradiation to other eye (1), fragilitas osseum (1), thyrotoxicosis (1), degenerative osteoarthritis (2), ankylosing spondylitis (1)
In nodular anterior scleritis seven patients had other diseases—for example, Cogan's syndrome (3), thyrotoxicosis (2), ophthalmia nodosa (1), hypertension (1)
One patient with necrotizing scleritis had hypertension as the only other systemic disease. There was no other evidence of a generalized systemic vasculitis

micus and episcleral disease. This phenomenon of late appearance of scleral disease was observed in seven of the 20 patients (35 per cent).

Laboratory investigations

The various laboratory investigations carried out in these patients are mentioned on page 165.

In the latter part of the series plasma protein estimations and electrophoresis were performed routinely in all patients with scleritis, and an immunological survey performed by the Immunology Department of the University of Glasgow. Although these results apply only to those patients who were seen during the last nine months of the analysis, they are shown in Table XIII because they showed

Table XII *Laboratory investigations: abnormal findings in patients*

Test	*Episcleritis*		*Scleritis*	
	No.	*(per cent)*	*No.*	*(per cent)*
Erythrocyte sedimentation rate	22	14	76	37
White blood count	7	4	14	7
Latex test for rheumatoid factor	12	7	28	13·5
Wassermann reaction	1	0·6	6	3
Uric acid	18	11·3	14	7

that a more sophisticated survey would reveal evidence of immunological abnormality not revealed by routine laboratory testing.

Of the 48 patients with scleritis, 27 (56 per cent) had some positive result in the immunological test. Eight patients had more than one positive result. These are presented with a control series of 30 patients matched for age and sex, with eye disease but with no scleral or uveal involvement.

Of the 12 patients with a positive result in the rheumatoid arthritis latex agglutination test, only two had clinical rheumatoid arthritis.

Skin tests

Intradermal or prick tests—inhalant, mould, fabric, dusts, and pollens—were performed in 30 patients with episcleritis, particularly those who gave some history of allergy. Mild reactions were detected to several agents in eight patients, but no overall pattern of allergic response as judged by this response could be detected. Two patients gave a history of a flare-up of episcleritis when in contact with printer's ink. The results of intradermal, patch and prick tests were negative, but vapour exposure produced flushing of the episclera.

X-ray examination

X-ray examination of the chest and sacro-iliac joints was carried out routinely in all patients with scleritis unless there was some contraindication. The seven-day rule with regard to ovulation was applied. Other examinations were carried out if indicated. Of patients in this series 42 per cent were intensively investigated by Fowler (1970), who found sacro-iliac abnormalities in seven, of whom three had definite ankylosing spondylitis. Only one patient had symptoms which would have led to this diagnosis without specific examination.

Electrodiagnostic investigations

Electro-oculograms (EOG) were performed initially in all patients; later in the series they were performed if the patient had severe disease or posterior scleritis. In 71 consecutive patients with episcleritis and scleritis presenting in the scleritis clinic, 13 had subnormal EOGs in the affected eye. All but one of these patients had scleritis but this was not severe in every case. The other patients had recurrent episcleritis and glaucoma.

Tissue biopsy

Biopsy of scleral tissue is not recommended unless there is great difficulty in diagnosing the eye condition or the underlying systemic disease. Episcleral biopsies were performed on three patients to try to elucidate the underlying disease. Two showed infiltration of the tissue with chronic inflammatory cells including occasional plasma cells, but no changes specific to any other disease. One revealed a lymphomatous infiltration of the episclera.

Treatment (see pages 187 to 189)

The various medical treatments given for scleritis and episcleritis are summarized in Tables XIV and XV. Recently oxyphenbutazone (Tanderil) ophthalmic ointment has been used in episcleritis and has been the subject of a double-blind controlled trial (Watson, McKay, Clemmett, and Wilkinson, 1973), but it was not used in the patients in this series.

Surgical treatment

Three cataracts have required extraction in the

Table XIII *Tissue antibody responses*

Patients	*Antinuclear factor*	*Rheumatoid factor (latex)*	R_3	*Thyroid antibody*	*Tanned RBC*	*Smooth muscle*	*Gastric parietal*	*Raised γ-globulin*
Scleritis (48)	3	12	2	5	2	7	6	4
Control (30)	0	0	0	2	0	1	2	0

presence of active scleritis. No complications followed these operations.

Four patients have had corneo-scleral grafts for descemetocele formation, expansion of the globe, increasing corneal guttering, and threatened perforation (Fig. 19). All have done well.

Two patients were given scleral grafts to cover thin sclera. The graft remained in place in one; in the other patient the graft became involved by scleritis and eroded away, leaving the choroid covered by a thin layer of conjunctiva. The course of the scleral disease was not influenced by the grafting.

Table XIV *Treatments given in episcleritis*

Treatment	*Simple episcleritis*	*Nodular episcleritis*
Not known	2	3
Placebo	6	0
Local prednisolone drops	80	17
Systemic prednisolone	2	1
Systemic sintisone	3	2
Systemic other steroid	0	0
Systemic antibiotics	0	0
Systemic oxyphenbutazone	22	2
Systemic indomethacin	2	2
Other systemic treatment for example, aspirin	4	1
Local steroid with systemic steroid	10	4
Local steroid with systemic oxyphenbutazone	17	9
Local steroid with systemic indomethacin	5	0
Other antibiotics	17	6

Enucleation

Scleritis is a serious condition and even if fully and carefully treated can lead to the loss of the eye, as indeed happened in three of the patients in this series. Only one of these patients was seen early in the disease and she was not able to tolerate steroid treatment; the eye was removed for intractable pain after the necrotizing disease had spread inexorably around the globe. The vision was preserved until the last area of undamaged sclera became involved, but then fell rapidly from 6/18 to hand movements within a week. Another eye was removed because it was blind and extremely painful. The third patient had severe keratolysis and necrotizing scleritis with loss of corneal and scleral tissue when first seen. Attempts at covering these defects by grafting failed and the eye was eventually removed.

Follow-up

Of the 159 patients with episcleritis and the 207 patients with scleritis, 146 (91 per cent) and 186 (90 per cent), respectively, have been followed-up during a period of between one and eight years (mean 5·8 years). All the patients who had not attended the clinic for six months and had had the disease for at least one year were sent a questionnaire in an attempt to determine the recurrence rate. Altogether 332 patients, of 366 who were circularized (91 per cent), replied to the questionnaire or returned to the clinic for follow-up.

In cases in which scleritis was seen in the initial stages and fully treated the recurrence rate was only 20 per cent. The recurrence rate was higher in those patients with anterior diffuse scleritis than

Table XV *Treatments given in scleritis*

Treatment	*Anterior*				*Posterior*
	Diffuse	*Nodular*	*Necrotizing*	*Scleromalacia perforans*	
Not known	2	7	0	0	0
Placebo	0	0	0	0	0
Local steroid	22	34	0	1	0
Systemic prednisolone	10	7	1	2	0
Systemic sintisone	7	12	0	0	0
Systemic antibiotics	0	1	0	0	0
Systemic oxyphenbutazone	7	5	2	2	0
Systemic indomethacin	4	1	0	0	1
Other systemic treatment	1	1	0	0	0
Local steroid with systemic steroid	19	14	7	5	2
Other systemic steroid	0	0	0	0	0
Local steroid with systemic oxyphenbutazone	17	21	5	0	2
Local steroid with systemic indomethacin	4	4	0	0	0
Other combinations	26	27	14	3	1

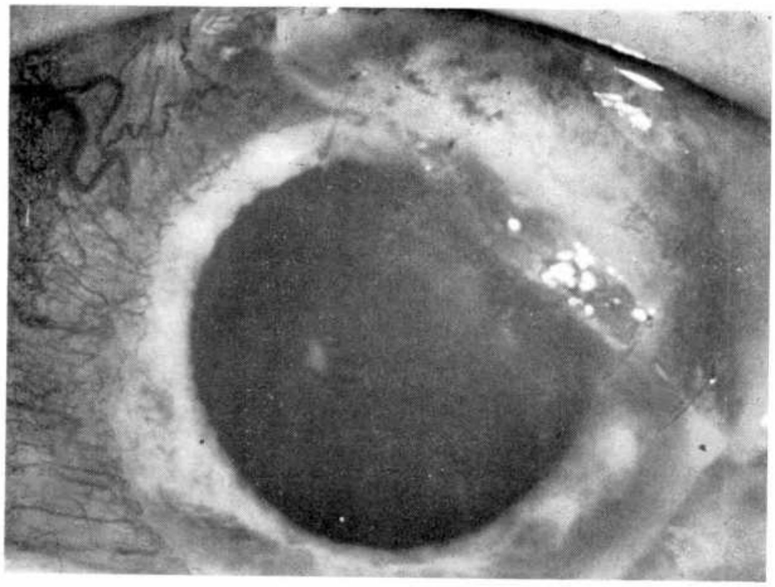

FIG. 19 *Overlay corneo-scleral lamellar graft on same patient as in Fig. 15 whose astigmatism was reduced from 15D to 6D by this procedure. Grafting only adds supporting tissue and does not affect underlying pathology*

with any other variety. The recurrences were also more severe in scleritis than episcleritis, 60 per cent of them requiring further hospital treatment.

It is important to follow up those patients with necrotizing disease because the disease can continue to progress when they are symptom-free, and they may require continuous treatment even when the disease is quiescent.

In episcleritis, however, each attack is self-limiting and usually clears without treatment. This has been confirmed in a double-blind controlled trial (Watson and others, 1973) in which each attack varied from a few hours to several days, the average being about seven days. Episcleritis was most common in the interpalpebral region, often changing from one side to the other with each attack. However, some patients always developed the inflammation at the same site although recurrences of both episcleritis and scleritis could occur up to 30 years after the onset of the disease (Table XVII).

Two-thirds of the patients had recurrences up to six years after the onset of the disease, but after this the recurrence rate fell. We found that there was often a considerable interval between the onset of the disease and the first attendance of the patient, who often came only because of apprehension caused by the recurrent attacks rather than the severity of the symptoms.

Deaths (Table XIX)

Of the 14 patients who were known to have died during the period of follow-up, only two had episcleritis. One died as a result of a road accident, and the other committed suicide. Of the remaining patients, six (43 per cent) had had necrotizing scleral disease, one diffuse anterior scleritis, and five nodular scleritis. None of the patients with scleromalacia perforans was known to have died during this period, although many of these patients

Table XVI *Duration of disease*

Disease	*Months*		*Years*					
	6	18	3	6	10	15	20	30
Episcleritis	6	35	24	17	11	29	0	4
Scleritis	10	34	24	19	6	1	0	6

Table XVII *Percentage of recurrences*

				Both eyes	
Recurrence	*Total*	*Same eye*	*Other eye*	*Simultaneously*	*At different times*
Episcleritis	64	46	5	27	22
Scleritis	69	48	4	31	15

Table XVIII *Severity of recurrences (per cent)*

		Treatment needed		
Disease	*Not severe*	*At hospital*	*By own doctor*	*By self-medication*
Episcleritis	31	38	26	4
Scleritis	27	60	13	1

Table XIX *Cause of death in the 14 patients who died during the period of follow-up*

Patient	*Sex*	*Type of scleritis*	*General conditions*	*Cause of death*
1	Female	Necrotizing	Rheumatoid arthritis Cardiovascular disease	Coronary thrombosis
2	Female	Necrotizing	Rheumatoid arthritis	Bronchopneumonia
3	Male	Necrotizing	Diffuse connective-tissue disease Chronic nephritis Hypertension	Cerebral haemorrhage
4	Female	Necrotizing	Hypertension	Cerebral haemorrhage
5	Female	Necrotizing	Bronchitis Emphysema	Congestive heart failure
6	Male	Necrotizing	Pulmonary tuberculosis Emphysema Bronchiectasis	Bronchopneumonia
7	Male	Diffuse anterior	Polyarteritis nodosa	Gastrointestinal haemorrhage
8	Male	Nodular	Rheumatoid arthritis	Coronary thrombosis
9	Male	Nodular		Myocardial infarction
10	Male	Nodular	Old herpes zoster ophthalmicus	Myocardial infarction
11	Male	Nodular	Old herpes zoster ophthalmicus	Myocardial infarction
12	Male	Nodular		Stabbed to death
13	Male	Nodular		Suicide
14	Male	Simple episcleritis		Road accident

had long-standing rheumatoid arthritis and were generally unwell at the time of their initial examination. Unfortunately three of these patients were not found for follow-up and might well have died in the interim. Of those who died of natural causes, 54 per cent had necrotizing disease, and 27 per cent of the patients with severe necrotizing scleritis were dead within eight years of the onset of the scleritis.

Five of the patients who died were known to have had diffuse connective-tissue disease; 21 per cent of all those with connective-tissue disease in this series. Another had hypertension and, it was thought, could have had a systemic vasculitis. As no necropsy was performed this could not be confirmed.

Discussion

While scleritis is an uncommon disease, accounting for only 0·08 per cent of new referrals to eye departments (Williamson, 1974), of those with the necrotizing disease 21 per cent died within eight years of the onset. The presence of scleritis may therefore portend serious systemic disease. Early diagnosis may lead to early treatment of the general condition, prolonging and probably improving the quality of life for these patients.

In our present series 46 per cent of the patients with scleritis had a known associated systemic condition. Of these, 15 per cent had definite connective-tissue disease, confirmed by a rheumatologist (Table XI). This incidence has recently been confirmed in an analysis of a further 88 patients with scleritis, in whom the incidence of associated systemic disease was 42 per cent, of which 15 per cent consisted of connective-tissue diseases.

It has been suggested in the literature (Duke-Elder and Leigh, 1965) that rheumatoid arthritis is the commonest single associated condition, but it was found in only 10 per cent of our patients. Scleritis also occurs in association with other connective-tissue diseases—systemic lupus erythematosus, polyarteritis nodosa, relapsing polychondritis, Wegener's granulomatosis—thus reflecting the collagenous nature of the tissue of which the sclera is composed. Altogether 31 patients (15 per cent) were found to have manifest connective-tissue disease; in seven of these the scleritis was the presenting feature. In 19 other patients there were conditions thought to have been immunologically induced, including two who had erythema nodosum. A total of 40 had positive latex agglutination tests for rheumatoid arthritis and a positive antinuclear factor, and if all the immunological tests are included, 72 patients (35 per cent) in the series tested had some abnormality of this type.

It seems that necrotizing scleral disease represents a different phase of scleritis in certain patients. In some patients who have had recurrent scleral disease for many years the scleritis has changed in type, coinciding with a change in the character of the systemic disease—for example, the onset of vasculitis in rheumatoid arthritis and renal disease in systemic lupus erythematosus. In other patients the onset of disease is 'malignant' with progressive and inexorable destruction of scleral tissues if treatment is not adequate. The mortality in this group is very high. Finally, there appears to be yet another type of scleral disease, scleromalacia perforans, which is almost completely confined to women, half of whom have long-standing rheumatoid arthritis. In these sequestration of the sclera occurs without warning and little, if any, inflammation. This type of scleral reaction is neither the same as that found in other forms of scleritis nor does it necessarily have the same pathogenesis.

A biopsy is contraindicated in scleral disease because the sclera does not heal easily—a fact well known to surgeons performing detachment operations a few years ago when scleral surgery was the rule. Large scleral nodules often contain pultaceous material which, if released, exposes the underlying choroid, but they may heal with fibrosis if left alone (Watson, 1974). Much of our knowledge of the underlying processes has therefore to be derived from the few biopsy specimens which have become available, and from those eyes which have been enucleated for severe disease (Sevel, 1967; Verhoeff and King, 1958; Anderson and Margolis, 1952; François, 1970; Henkind, 1974). This unfortunately means that we can find out little about the disease in most of the patients other than what can be deduced from their clinical examination and serological investigations. Biopsy of the episcleral lesions showed oedema, separation of the episcleral fibres, infiltration with lymphocytes, and some cuffing of the vessels. Henkind and Gold (1973) observed a rheumatoid nodule in the episcleral tissue but we have not seen this. It is certain, however, that the changes typical of rheumatoid nodules occur in the sclera in certain patients with necrotizing scleritis and rheumatoid arthritis. More typical, however, is a granulomatous reaction in the sclera, similar to that found elsewhere in the body in connective-tissue disease, the predominant feature being fibrinoid necrosis. Similar lesions can be produced in animals with the Schwartzmann reaction. It was probable therefore that in many cases the altered immunity in the patient was the underlying cause of this condition. The sclera is also involved in gout, in which the response is due to inflammation caused by proteolytic enzymes released from polymorphs which have ingested uric acid crystals.

The chronic granulomatous diseases of bacterial origin have also been quoted as a cause of scleritis (Duke-Elder and Leigh, 1965). We saw only two patients with active pulmonary tuberculosis and scleritis, although ancient photographs and histological sections make it clear that this was a much commoner condition when tuberculosis was severe and less easily treatable. We have not knowingly seen scleritis in association with sarcoidosis.

Syphilis, however, can present as a scleritis. Four patients have presented in this way with the eye changes as their only symptom. They were found to have severe active syphilis with a positive cerebrospinal fluid serological result. The scleritis disappeared when the syphilis was fully treated. Altogether 14 patients had a positive Wassermann reaction in this series, seven presented with simple episcleritis and the others with a diffuse anterior and nodular scleritis. The scleritis associated with syphilis and tuberculosis was in no way different from the other forms.

The aetiology of episcleritis is even more uncertain. However, two patterns are apparent. Most patients have intermittent bouts of moderate or severe inflammation at intervals of one to three months, lasting seven to ten days and occurring much more commonly during the spring and autumn than in the summer or winter. Only rarely can any certain precipitating factor be found, the attacks usually being related to family upsets and worries at work. Occasionally, however, a clear history of exogenous sensitization is given—for example, contact with printer's inks. In one instance the patient had only to be inside the printing works for his eyes to flare up; exposure to the vapours of the ink also produced an attack under hospital conditions, but skin tests gave negative results. 11 per cent of patients with episcleritis had recurrently high serum uric acid values (more than 6·5 mg per cent on three readings), and 7 per cent had clinical gout. 12 per cent also had a history of asthma and hay fever; only one patient related the attacks to menstruation. Two patients developed episcleritis after a desensitization vaccination.

The second group of patients gave no history of periodicity but rather of mild, prolonged attacks of inflammation. Into this category came almost all those patients who had some other intercurrent disease. Seven patients had a positive Wassermann reaction (one with active syphilis), four had mild rheumatoid arthritis with a positive rheumatoid factor but only a few joint symptoms, and two had erythema multiforme; the others had active tuberculosis, Henoch-Schönlein purpura, or rosacea. Herpes simplex virus has been grown from one lesion. The appearances of the episcleritis did not differ in these two groups, and in neither did the episcleritis progress to a scleritis except in those patients with herpes zoster who have already been discussed. General physical examination and chest *x*-ray failed to reveal any evidence of focal sepsis.

Herpes zoster involves both the cornea and sclera. As already discussed, an episcleritis may occur in the early vesicular stage of the disease, disappearing completely and then presenting as a deep localized scleritis at the site of the original lesion some two to three months later. Alternatively the sclera may be involved early in the disease, in which case a nodular scleritis is the rule.

Clinical gout was found in five patients who presented with episcleral and scleral disease, and 32 had raised levels of uric acid on more than one occasion. The serum uric acid is a notoriously unreliable test and a single positive recording should not be taken as indicative of underlying gout. It was observed that those patients with clinical gout and scleral and episcleral disease had deposits of uric acid beneath the conjunctiva around the anterior ciliary vessels at the plica. It was hoped that this could be used as a diagnostic sign, but deposits which look almost identical are frequently seen in patients whose serum uric acid is normal.

It could be suggested that this group of patients with episcleritis may represent the earlier stages of a benign form of scleritis. If this was so, one would expect a significant number of cases to progress from episcleritis to scleritis, but during the eight-year period of follow-up we did not see this. We did see three patients who had episcleritis in one part and scleritis in another part of the same eye. However, it is an interesting and definite observation that the episcleritis did not progress to scleritis even during a prolonged follow-up. We feel that this suggests that episcleritis and scleritis are two different types of reaction to a similar antigen within the different tissues. Thus the fact that the episclera is involved in the course of the disease does not mean that the underlying sclera would become involved, even after a long period of time. We have, as yet, no definite evidence that scleritis is an autoimmune disease, and the evidence presented in this paper is only circumstantial. Equivalents of Koch's postulates which need to be satisfied for auto-immune disease are as follows (Glynn, 1974):

1. There must be a specific antigen. It may not be from the tissue involved in order that complexes may be formed elsewhere. In general, one would expect the antigen to be found at the site of the lesion, for instance the thyroid antigen in autoimmune thyroiditis. It should be possible to:
2. Extract the antigen.
3. Reproduce the disease in some experimental animal.
4. Demonstrate specific antibodies to the antigen or specifically sensitize cells reacting with antigen.

We were not able to fulfil these postulates partly because of the undesirability of obtaining biopsy tissue in our patients, and because of uncertainty that the disease produced in animals was of the same nature. However, the circumstantial evidence from the well-proven association with known connective-tissue disease is strongly suggestive that this is a manifestation of immune complex disease in a large number of cases. In herpes zoster ophthalmicus and gout the precipitating cause is known, but until more is known about the precipitating factors of the immune-complex disease we are not justified in making any further conclusions.

Whatever the pathogenesis might be, we found that by careful differential diagnosis we were able to treat the disease appropriately and adequately so as to prevent a serious destructive change taking place in the eye. The differential diagnosis of scleritis and episcleritis is summarized in Table XX.

TREATMENT

Apart from the very few patients in whom a specific bacterial or viral agent could be found to

Table XX *Cardinal features in the differentiation of scleritis from episcleritis*

	Episcleritis		*Scleritis*				
			Anterior				*Posterior*
	Simple	*Nodular*	*Nodular*	*Diffuse*	*Necrotizing*	*Scleromalacia perforans*	
Onset	Sudden	Usually sudden	Gradual	Gradual	Gradual	Insidious	Gradual
Redness	Bright red	Red	Dusky red	Bluish red	Bluish red	Very slight	Variable
Pain	Slight localized	Slight localized	Moderate, localized and referred	Moderate, localized and referred	Severe, localized and referred	Slight, if any	Severe, localized and referred
Photophobia and lacrimation	Occasionally	Occasionally	Occasionally	Occasionally	Common	None	Unusual
Vascular changes	Superficial episcleral	Superficial episcleral	Superficial and deep episcleral	Superficial and deep episcleral	Superficial and deep episcleral and occasionally avascular patch	Avascular area	Superficial and deep episcleral
Chemosis	Occasionally	Rare	Rare	Common	Variable	Absent	Common
Scleral thinning or transparency	Rare	Rare	Common	Common	Common	Always	Rare
Visual acuity	Normal	Normal	Normal	Occasional loss	Common loss	Common loss	Very common loss

have caused episcleritis or scleritis, the treatment is suppression of the inflammation in order to relieve the discomfort and prevent the destructive changes which may accompany the inflammation. Treatment, which must be continued until the disease has followed its natural course, has proved to be effective and many eyes are being saved or prevented from developing severe complications. Only three eyes (0·6 per cent) were lost—one that of a patient who could not tolerate the treatment rather than because of the severity of the eye disease.

EPISCLERITIS

As the condition is self-limiting, harmless, and frequently symptomless, treatment may not be necessary. Double-blind controlled studies have been conducted to determine first whether any treatment was necessary and secondly which drugs were most effective in suppressing the inflammation.

In this trial some patients received placebo, others local steroid ointment, and the remainder oxyphenbutazone ointment. All the patients recovered within 10 days. Both oxyphenbutazone eye ointment and betamethasone ointment appeared to hasten the recovery by about one day, but the differences were not significant (Watson and others, 1973) (Fig. 20).

If it is felt necessary to treat the patient, either because of the symptomatology or because of multiple recurrences, we recommend the following routine:

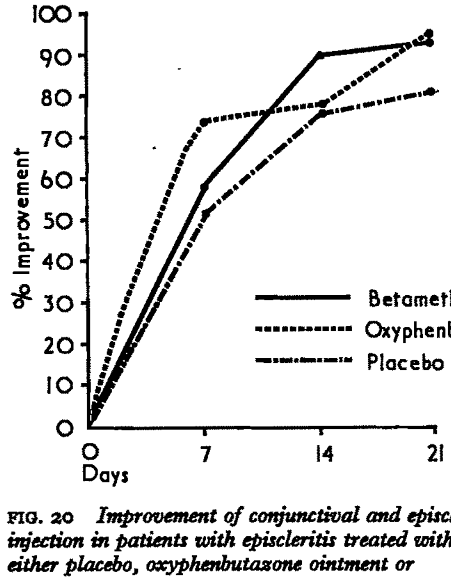

FIG. 20 *Improvement of conjunctival and episcleral injection in patients with episcleritis treated with either placebo, oxyphenbutazone ointment or betamethasone 1 per cent ointment. Although those treated with active substances improved slightly faster, 80 per cent of those receiving placebo had recovered by 21 days*

Topical medication: Any one of the following medications may be used:

1. *Prednisolone* eye drops 0·5 per cent hourly until 24 hours after the inflammation has subsided, then reduced to three times a day for a further four days.
2. *Betamethasone* (Betnesol) eye ointment 1 per cent four times a day during the attack, and for a further week after the attack has subsided.
3. *Oxyphenbutazone* (Tanderil) eye ointment 10 per cent four times a day during the attack, and for a further week after the attack has subsided.

Systemic therapy: Occasionally patients will not respond adequately to local therapy, in which case systemic oxyphenbutazone, indomethacin (Indocid), or corticosteroid may be needed.

1. *Oxyphenbutazone:* 600 mg daily in divided doses is given until there is a response. The dose is then reduced to 400 mg until the eye is quiet and then it is stopped. This treatment is given in addition to local treatment.
2. *Indomethacin:* If the patient fails to make a rapid recovery the drug may be changed to indomethacin 100 mg daily in divided doses, and then reduced to 75 mg as soon as there is a response. A double-blind controlled study just completed indicates that oxyphenbutazone and indomethacin are equally effective as anti-inflammatory agents, although some patients respond better to one drug than the other.
3. *Corticosteroids:* In the rare case which does not respond to local treatment, or systemic oxyphenbutazone or indomethacin, it is justifiable to give a short, intensive course of prednisolone or its equivalent. A suppressive dose for this condition is 60 mg prednisolone daily which, as soon as the inflammation starts to regress, can be reduced rapidly with a view to withdrawing the drug entirely within one month.

A double-blind controlled study was carried out in these patients (Watson, Lobascher, Sabiston, Lewis-Faning, Fowler, and Jones, 1966) which revealed that both oxyphenbutazone and prednisolone were effective, but that patients receiving systemic prednisolone had a rebound of their symptoms, while those having oxyphenbutazone remained symptom-free.

SCLERITIS

Because of the depth and severity of the inflammation local steroid treatment is ineffective. Drops or ointment are soothing and reduce the inflammation but are not sufficient to control the scleritis.

As a result of our experience we have come to the conclusion that the following regimen of treatment is the most likely to be effective:

As soon as scleritis is diagnosed:

Systemic oxyphenbutazone 600 mg daily in divided doses for four days, followed by 400 mg daily until the condition is suppressed. This dosage is continued for one week after all symptoms have subsided. Or

Systemic indomethacin 100 mg daily in divided doses, reduced to 75 mg daily in divided doses as soon as there is a response. Treatment is continued until the condition has been quiescent for seven days.

These two drugs appear to be more effective than any of the other anti-inflammatory agents in general use—for example aspirin, ibuprofen (Brufen), etc.

Local steroids

Usually prednisolone or betamethasone can be given in addition.

Subconjunctival steroids are not recommended in scleritis

We have seen two patients in whom extreme thinning has occurred at the site of a subconjunctival injection of steroid (Watson, 1974; Fraunfelder and Watson, 1976). It is not certain whether it is the vehicle in which the steroid is contained or the steroid itself which is the irritating factor. We have from time to time given intraorbital steroid injections in patients unable to take steroid systemically. The effect is transient and the injections have to be repeated weekly to be effective. Most patients will not tolerate this regimen and so it is not satisfactory for routine use.

Systemic corticosteroids

If the scleritis is very severe, and does not respond to the oxyphenbutazone or indomethacin within a week, or if any avascular areas appear in the episclera, systemic steroids must be given in heavy suppressive doses. The sclera is avascular and high concentrations are required to produce a therapeutic effect.

Systemic prednisolone

80 mg a day in divided doses is usually sufficient as an initial dose. If it is effective the response is dramatic; although there is little change in 24 hours or even 48 hours, the pain disappears. The eye signs may not improve for a further 48 hours, after which time they rapidly regress. As soon as the condition is brought under control the dosage can be dropped within a week to a maintenance level which is usually between 10 and 20 mg prednisolone daily. Cautious reduction from this level usually enables the patient to be taken off the drug or to be maintained with another anti-inflammatory agent within three to four weeks. In patients who have been unable to tolerate, or have failed to respond to, prednisolone, occasionally a response can be obtained with Sintisone (prednisolone 21-stearoylglycolate), eight tablets (each tablet containing 0·63 mg) daily in divided doses (Hayreh and Watson, 1970). Why this preparation is so effective is uncertain, but we have several patients who have to be maintained on it rather than on the conventional steroids.

Surgery

Surgery is very rarely necessary in scleral disease. Provided the condition is seen early and treated vigorously, scleral necrosis can be largely prevented. Corneal grafting has had to be performed in four patients because of threatened perforation, an expanding globe, for peripheral corneal guttering, and for descemetocele. The corneal grafts have taken well and in all cases the scleritis has become less severe after this was done.

Many reports appear in the literature of scleral grafting for scleromalacia perforans (Holthouse, 1893; Ashton and Hobbs, 1952; Torchia, Dunn, Pease, 1968; Vancea, Vancea, Jalobceastii, Colev, and Calin, 1971; Sevel and Abramson, 1972; and others). This has been necessary in only two patients in this series—neither of whom could tolerate steroids. In both patients the graft took well. In one the whole necrotic area was removed and the residual area of scleral inflammation could be controlled with local steroids and oxyphenbutazone systemically. In the other the necrotizing process continued from the edge of the scleral overlap and the eye was eventually lost, no other medical treatment being tolerated.

We consider scleritis to be a medically treatable condition, and provided the dosages of the drugs are adequate to suppress the inflammatory change, the condition will be controlled. In this we disagree with Sevel and Abramson (1972) and Aronson and Elliott (1974). We feel our results justify our claim.

Summary

The data from 159 patients (217 eyes) with episcleritis and 207 patients (301 eyes) with scleritis have been investigated in detail and the results analysed with the help of a computer. Of these patients, 91 per cent were followed-up during a

period of one to eight years. A new classification is presented which is as follows:

Episcleritis (217 eyes)
Simple episcleritis (170 eyes)
Nodular episcleritis (47 eyes)
Scleritis (301 eyes)
Diffuse anterior scleritis (119 eyes)
Nodular anterior scleritis (134 eyes)
Necrotizing scleritis (42 eyes). Of these, 13 were regarded as scleromalacia perforans.
Posterior scleritis (6 eyes)

The diagnosis is based on an exact clinical examination which is fully described.

Episcleritis has been shown to be a benign recurring condition, a mild keratitis being the only occasional complication. Episcleritis does not progress to scleritis, except in the case of herpes zoster which sometimes starts as an episcleritis with the vesicular stage of the eruption, to reappear three months later as a scleritis in the same site.

No clear conclusions could be drawn as to the aetiology of episcleritis.

Scleritis is always accompanied by episcleral inflammation which must be ignored in making the diagnosis. Scleritis is a much more severe disease than episcleritis, leading to loss of visual acuity from corneal changes, uveitis, cataract, or retinal detachment if not treated. Necrotizing scleritis with inflammation is the severest form of the disease and 21 per cent of the patients with this condition died within the eight-year-period of follow-up.

Connective-tissue disease was the commonest associated general condition; the incidence of necrotizing scleritis was higher in this group and 21 per cent of these patients were among those that died. It is probable that necrotizing scleritis represents the eye changes of the malignant phase of systemic connective-tissue disease.

Treatment is unnecessary in episcleritis but in scleritis systemic treatment with anti-inflammatory agents or corticosteroids is obligatory. Using these routines of treatment only three patients (0·6 per cent) have lost an eye.

Apart from ourselves, the following have worked in the Scleritis Clinic during the past 10 years: A. Atkinson, P. Awdry, P. E. Cleary, R. S. Clemett, P. Fowler, A. Freedman, B. Hazleman, P. Henderson, A. D. Holt-Wilson, D. Jones, S. Lachmann, D. Lloyd-Jones, D. Lobascher, A. J. Lyne, and D. A. R. Mackay, and we would like to thank them all for their help and ideas. We are sure many of these ideas are incorporated in this article but it is impossible to acknowledge them properly because we have forgotten where they originated. We should also like to thank all those surgeons who have referred patients to us: without them there would be no clinic.

The computer analysis was completed at the Institute of Ophthalmology and many of the illustrations were reproduced there; the rest were done in the Medical Illustration Department of Addenbrooke's Hospital, Cambridge.

Figs 6 and 14 were reproduced from the *Transactions of the Ophthalmological Society of the United Kingdom*; Fig. 16 from Connective-tissue disease in the eye, in *Recent Advances in Ophthalmology*, ed. P. Trevor-Roper, published by Blackwell; and Fig. 20 from the *British Journal of Ophthalmology*.

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Episcleritis and scleritis

A study of their clinical manifestations and association with rheumatoid arthritis

D. D. M. McGAVIN, J. WILLIAMSON, J. V. FORRESTER, AND W. S. FOULDS
Tennent Institute of Ophthalmology and Southern General Hospital, Glasgow
W. W. BUCHANAN, W. C. DICK, P. LEE, R. N. M. MACSWEEN, AND K. WHALEY
Centre for Rheumatic Diseases, Glasgow

Sir William Read, Royal Ophthalmologist during the reign of Queen Anne (1702–1714), who incidentally was unable to read or write (Guthrie, 1958), gave a choice description of the dangers of perforation in deep scleritis: 'For it is most certain that this horny membrane . . . by how much deeper the blister is hidden in the membrane . . . in danger to make an ulceration by breaking through the membrane, whereupon may ensue an utter loss and decay of all the humours'. Further documentation of the sequelae of scleral inflammation awaited a further century for the description of staphylomata by Scarpa (1818), who described two cases of posterior staphylomata found at necropsy. Mackenzie (1830) attributed scleritis to atmospheric conditions and suggested the term 'sclerotitis atmospherica' or 'rheumatic ophthalmia'. Later Mackenzie (1854) was to suggest the name 'sclerotitis idiopathica'. Wolfe (1882), lecturing to the students of Anderson College, Glasgow, used the currently accepted nomenclature of episcleritis and scleritis. The later terminology has been excellently recorded by Sevel (1967).

Earlier authors often associated inflammation of the sclera with rheumatic disease (Mackenzie, 1830; Littell, 1840; Wolfe, 1882; von Arlt, 1885). Besides 'rheumatism', scleritis was attributed to gout (Cleobury, 1826; Walton, 1875), mercury poisoning (Morgan, 1839), venereal disease, particularly syphilis (Morgan, 1839; von Arlt, 1885); scrofula (Mackenzie, 1854); excessive exposure to varying atmospheric conditions (Mackenzie, 1830; de Schweinitz, 1899), and menstrual derangement (de Schweinitz, 1899).

The most consistent systemic disorder associated with episcleritis and scleritis, particularly the latter, is rheumatoid arthritis (Van der Hoeve, 1934; Verhoeff and King, 1938; Smoleroff, 1943; Edstrom and Osterlind, 1948; Mundy, Howard, Stillman, and Bevans, 1951; Hollenhorst and Henderson, 1951; Watson and Lobascher, 1965; Watson, 1966; Lyne and Pitkeathly, 1968; Fowler, 1970; Jayson and Jones, 1971), and with this in mind the present study differentiates rheumatoid episcleritis and scleritis from non-rheumatoid episcleritis and scleritis according to the criteria for 'classical' or 'definite' rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959).

Material and methods

Examination of patients was carried out at two centres: the Centre for Rheumatic Diseases, Glasgow, and the Tennent Institute of Ophthalmology, Western Infirmary, Glasgow.

During the years 1965 to 1973 any patient seen at the Centre for Rheumatic Diseases with rheumatoid arthritis who had any eye complaint was referred to an ophthalmologist and any case of episcleritis or scleritis was examined in detail. Those patients examined before 1971 who were still alive were recalled to hospital or visited in their homes. It was at the beginning of 1971 that a scleritis clinic was instituted at the Tennent Institute, and a pro forma outlined the investigations to be documented for patients at both centres. In all patients these investigations included examination by an ophthalmologist and by a rheumatologist; this was supplemented by laboratory investigations appropriate to ocular inflammation and rheumatoid disease.

The purpose of the study was to compare patients who presented with rheumatoid disease, who subsequently developed episcleritis and scleritis, with patients who presented with episcleritis or scleritis in whom rheumatoid disease was incidental to their referral.

CENTRE FOR RHEUMATIC DISEASES

Between 1965 and 1973, 4210 patients with rheumatoid arthritis were examined at the Centre for Rheumatic Diseases. These patients satisfied the diagnostic criteria of the American Rheumatism Association (Ropes and others, 1959). Seven of these patients had episcleritis and 28 had scleritis.

TENNENT INSTITUTE OF OPHTHALMOLOGY

During 1971 and 1972, 62 patients were examined at the scleritis clinic: 35 of these patients had episcleritis and 27 had scleritis. Two of the patients with episcleritis and nine of the patients with scleritis had rheumatoid

Address for reprints: J. Williamson, Tennent Institute of Ophthalmology, Glasgow

arthritis according to the criteria already cited (Ropes and others, 1959).

The presentation of results initially gives the incidence of episcleritis and scleritis in rheumatoid arthritis, and also the incidence of rheumatoid arthritis in episcleritis and scleritis. Thereafter, unless it is otherwise indicated, the patients are divided into those with rheumatoid disease and those without rheumatoid disease. This results in four groups of patients with:

1. Rheumatoid episcleritis (nine cases)
2. Rheumatoid scleritis (37 cases)
3. Non-rheumatoid episcleritis (33 cases)
4. Non-rheumatoid scleritis (18 cases)

Comparisons are made between these four groups of patients. In the section dealing with the systemic manifestations of rheumatoid disease and also in some of the laboratory investigations a further comparison is made, that is, between the combined groups of rheumatoid episcleritis and scleritis and a group of rheumatoid controls, patients with rheumatoid arthritis matched for age and sex with the rheumatoid episcleritis/scleritis groups but without episcleral or scleral inflammation. This gives two further groups:

5. Rheumatoid episcleritis/scleritis (46 cases)
6. Rheumatoid controls (46 cases)

Statistical analysis is presented throughout the study. However, the numbers, in what is a relatively uncommon type of ocular inflammation, are often very limited. The biological meaning of statistical evidence therefore requires critical appraisal.

OPHTHALMIC EXAMINATION

Complaints of eye symptoms were elicited with as little prompting as possible. The duration of the condition was estimated from the first episode of inflammation. Accurate documentation of duration is difficult as it is not always certain that a condition which may persist intermittently during a period of some years has truly settled. Visual acuity was assessed by Snellen's test chart at the Tennent Institute with or without glasses as appropriate. Refraction was not done routinely.

The anterior segment of each eye was examined in diffuse light, often in ordinary daylight, and by detailed examination with a slit-lamp microscope. Patients seen in their homes were examined with a single loupe and focal light. Slit-lamp examination served to reveal the depth of inflammation, determining which network of vessels was predominantly affected. It is occasionally difficult to be certain whether an apparently nodular episcleritis is in fact a scleritis; the diagnosis is often more readily apparent in retrospect when, for example, an area of scleral translucency will indicate a scleritis. The greyish-blue colour of deep scleritis is due to the dark uvea becoming evident through translucent sclera. In contrast, episcleritis is usually bright red in colour. A careful slit-lamp examination after observation in diffuse light, with a conclusive diagnosis made only after observing the inflammation for varying periods of time, is sufficient in most cases to provide a diagnosis. Nevertheless, there remain a few cases in which it is impossible to differentiate with certainty an episcleritis from a superficial scleritis. The figures that are given, therefore, are not absolute, but the features associated with predominantly superficial inflammation affecting primarily the episclera will be contrasted with features of deeper involvement affecting primarily the sclera.

Ophthalmic examination took note of any corneal complications, anterior uveitis and cataract, particularly posterior subcapsular cataract. The fundi were examined after instillation of cyclopentolate hydrochloride BP 1 per cent. A Haag-Streit applanation tonometer recorded the intraocular pressure in patients seen in hospital, and a Perkins hand-held applanation tonometer was used for those patients who were visited in their homes.

Any suggestion of limitation of extraocular muscle movement or history of diplopia prompted referral to the orthoptist for a more exact record.

All patients were screened for evidence of keratoconjunctivitis sicca (KCS) by Schirmer's tear test (Schirmer I) using standardized filter-paper strips*. The length of wetting of the filter paper at the end of 5 minutes was measured. A normal tear secretion was accepted as 15 mm wetting or more for patients under the age of 40 years, and 10 mm wetting for patients over the age of 40 years, as standardized by Halberg and Berens (1967). All patients with reduced tear flow had a drop of rose bengal 1 per cent instilled into the eye, and punctate staining indicated the presence of dead or dying cells and excess mucus. Confirmation of KCS was given by Schirmer's test (Schirmer II) in which a 10 per cent ammonia solution is held approximately 15·2 cm below the nose to stimulate tear production, which is recorded as in Schirmer I.

GENERAL EXAMINATION

The following investigations were designed to measure the severity of any disease of the locomotor system, and complications of rheumatoid arthritis and other connective-tissue disorders.

For each patient were recorded four grades of functional incapacity (Steinbrocker, Traeger, and Batterman, 1949). The articular index, a summation index, estimated the number of involved joints and the severity of their involvement as judged by tenderness to pressure over the joint margin. Radiological evidence of the degree of bone involvement was categorized in four stages of increasing severity (Steinbrocker and others, 1949).

A number of extra-articular complications of rheumatoid disease were noted: subcutaneous granulomatous nodules, peripheral neuropathy, vasculitis manifest as skin ulceration or bruising, and tendon rupture. Atrophy of skin was recorded as a recognized side-effect of treatment with systemic corticosteroids (Scarborough and Shuster, 1960; Greenwood, 1966). An enlarged spleen suggested the possibility of Felty's syndrome (Felty, 1924), and evidence of amyloidosis was noted, as rheumatoid arthritis is now the commonest cause of secondary amyloidosis in western countries (Boyle and Buchanan, 1971).

Xerostomia and salivary gland enlargement were recorded as features associated with Sjögren's syndrome (Sjögren, 1933).

*Developed by Halberg and Berens (Crookes-Barnes Laboratories, Inc., Wayne, NJ, USA)

An electrocardiogram was used in most patients (unless bedridden and visited at home) to exclude cardiac disease, which has been noted as a complication in patients with scleritis and rheumatoid arthritis (Smoleroff, 1943; Jayson and Jones, 1971). Blood pressure recordings and cardiac auscultation screened patients for aortic incompetence, which has been associated with scleritis (Pitkeathly, Howitt, and Lyne, 1970).

All patients had a chest *x*-ray examination to exclude evidence of active tuberculosis or sarcoidosis and to demonstrate any pulmonary complication of rheumatoid arthritis.

LABORATORY METHODS

In each patient the haemoglobin concentration, erythrocyte sedimentation rate, and serum proteins, although nonspecific in nature, reflected the severity of disease. Haemoglobin estimation at the Tennent Institute of Ophthalmology was given as a percentage, but in the Centre for Rheumatic Diseases it was given in grams per 100 ml. For comparison of data each haemoglobin value in g/100 ml was converted to a percentage reading, taking 14 g/100 ml as a value of 100 per cent. Alkaline phosphatase, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase were recorded to assess any association of liver disease and scleritis. Liver disease has been noted in 6 per cent of patients with Sjögren's syndrome without rheumatoid arthritis and in 1·5 per cent of patients with Sjögren's syndrome and rheumatoid arthritis (Whaley, Williamson, Dick, Goudie, Nuki, and Buchanan, 1970). Serum uric acid levels were estimated to exclude gout. In view of the relevance of scleritis in venereal disease, usually syphilis (Cleobury, 1826; von Arlt, 1885; Holloway and Fry, 1931), the Wassermann reaction, Venereal Disease Reference Laboratory (VDRL) slide test and Reiter protein complement-fixation test (RPCFT) were performed. Further investigations included the antistreptolysin-O titre, and tests for evidence of brucellosis and toxoplasmosis. The antistreptolysin-O titre may be raised in erythema nodosum, a condition associated with episcleritis (McCarthy, 1961). Brucellosis, a well recognized cause of uveitis (Woods and Guyton, 1944; Hewson, 1964), has been incriminated in a case of scleritis (Thomas, Helluy, Cordier, and Algan, 1953) and to exclude it the complement-fixation, standard agglutination (direct), and antihuman globulin (Coombs') tests were performed. Cat, Marinoni, Giraldi, and Costa (1971) reported that two of their cases of juvenile rheumatoid arthritis had high false positive titres for toxoplasmosis, and accordingly the toxoplasma dye test (Sabin and Feldman, 1948) was routinely investigated.

A multiplicity of autoantibodies may occur in the connective-tissue (collagen) disorders (Copeman, 1964). Scleritis has been called a collagen disorder (Hayreh and Watson, 1970). In view of this, autoantibody screening tests were undertaken in each case. Tests were carried out for rheumatoid factor, using the latex agglutination technique (Hyland Laboratories) (Ziff, Brown, Lospalluto, Badin, and McEwan, 1956), the R_3 latex agglutination test (Denver Laboratories) using sera giving a positive result in the rheumatoid latex test, and by the tanned red-cell haemagglutination technique for thyroglobulin antibody (Fulthorpe, Roitt, Doniach, and Couchman, 1961). All the remaining autoantibody investigations applied the indirect immunofluorescent technique. These were tests for thyroid microsomal antibody, antinuclear factor, salivary duct antibody, mitochondrial antibody, gastric parietal-cell antibody, and smooth-muscle antibody (Table I).

The assay of complement C3 (1c/1a globulin) used specific immunodiffusion plates (Hyland Laboratories) and serum concentrations of IgG, IgA, and IgM globulins were similarly measured by radial immunodiffusion using commercially-prepared plates (Behringwerke) according to the method of Mancini, Carbonara, and Heremans (1965).

EYE SWABS

Platinum loop scrapings and swabs taken from the conjunctiva of the inflamed eye (the more inflamed in bilateral disease) in each case seen at the Tennent Institute of Ophthalmology were sent for investigation of bacteria, fungi, and viruses. Platinum-loop scrapings were plated on chocolate agar for bacteriology. Isolation of fungi was effected by platinum-loop scrapings plated on 2 or 3 per cent malt extract agar with chloromycetin 0·05 mg/ml. Swabs for virus studies were placed immediately in Eagle's tryptose phosphate medium with calf serum 10 per cent.

TYPE I ALLERGY (ATOPY)

Lyne and Pitkeathly (1968) with J. W. Kerr and J. M. MacLeod noted that, in 25 of 33 cases having single attacks of episcleritis, the inflammation affected the interpalpebral area. The findings in this present study endorse their report and it seemed worth considering external aggravating factors in the category of immediate hypersensitivity. Altogether 23 patients, all of them with non-rheumatoid inflammation, and all except six cases of episcleritis, were subjected to skin testing for house dust, grass pollen, alternaria, feathers, house dust mite, *Aspergillus*, *Candida albicans*; and cat and dog hair, if one of these pets was in the home.

Table I *Autoantibody investigations*

Autoantibody	*Tissue substrate*	*Reference*
Thyroid microsomal	Human toxic thyroid	Holborow, Brown, Roitt, and Doniach (1959)
Antinuclear factor	Rat liver	Beck (1961)
Salivary duct	Human salivary gland	MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson (1967)
Mitochondrial	Rat kidney	Goudie, MacSween, and Goldberg (1966)
Gastric parietal	Human gastric mucosa	Adams, Glen, Kennedy, McKenzie, Morrow, Anderson, Gray, and Middleton (1964)
Smooth muscle	Rat stomach smooth muscle	Johnson, Holborow, and Glynn (1965)

MORTALITY

An initial impression suggested that more of the patients with rheumatoid episcleritis or scleritis had died since examination as compared with the group of rheumatoid controls. The control group was carefully matched for age, sex, and year of presentation at the Centre for Rheumatic Diseases. Contact with the general practitioner of each patient determined which patients had died by February 1974. The Registrar of Births, Deaths and Marriages, Glasgow, provided information as to the cause of death in each case.

Results

INCIDENCE (Table II)

Between 1965 and 1973, 4210 patients with rheumatoid arthritis were examined at the Centre for Rheumatic Diseases. Seven of these patients had episcleritis (0·17 per cent) and 28 patients had scleritis (0·67 per cent).

Table II *Incidence of episcleritis and scleritis in rheumatoid arthritis*

Clinic	*Disease*	*Cases*	*No. of patients with rheumatoid arthritis*	*Percentage*
Centre for Rheumatic Diseases 1965–73	Episcleritis Scleritis	7 28	4210 4210	0·17 0·67
Scleritis Clinic, Tennent Institute of Ophthalmology 1970–71	Episcleritis Scleritis	35 27	2 9	5·7 33·3

Thirty-five cases of episcleritis and 27 cases of scleritis presented at the Tennent Institute of Ophthalmology during 1971 and 1972. Two of the cases of episcleritis (5·7 per cent) and nine of the cases with scleritis (33·3 per cent) had clinical and radiological evidence of rheumatoid arthritis according to the diagnostic criteria of the American Rheumatism Association (Ropes and others, 1959). Each of these cases was sero-positive for rheumatoid factor. One further case of episcleritis and six further cases of scleritis were weakly sero-positive for rheumatoid factor, but had no clinical or radiological evidence of rheumatoid arthritis.

(Unless otherwise indicated in the remaining data patients from both clinics with rheumatoid arthritis are combined and compared with the findings of patients without rheumatoid arthritis.)

AGE, SEX, AND BILATERALITY (Tables III*a–f*)

The only group of patients with a mean age outside the sixth decade was the non-rheumatoid episcleritis group which had a mean value of 45·1 years.

All cases with rheumatoid episcleritis were female and this was consistent with the higher incidence of rheumatoid arthritis in women. Scleritis was found in twice as many women as men (67·6 to 32·4 per cent). It is interesting to note that of the non-rheumatoid patients, episcleritis was found equally in women and men (48·5 and 51·5 per cent), but scleritis showed a marked preponderance in women (83·3 to 16·7 per cent).

The 9 patients with rheumatoid episcleritis

Table IIIa *Age (rheumatoid episcleritis and rheumatoid scleritis) 46 cases*

Disease	*Cases*	*Age range (years)*	*Mean (years)*	*SD*	*SEM*
Episcleritis	9	54–69	58·7	±5·9	±2·0
Scleritis	37	28–77	58·3	±11·8	±1·9

Statistical analysis: $t = 0{\cdot}0840$; P = NS

Table IIIb *Age (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases*

Disease	*Cases*	*Age range (years)*	*Mean (years)*	*SD*	*SEM*
Episcleritis	33	20–71	45·1	±14·6	±2·5
Scleritis	18	32–75	53·2	±13·7	±3·2

Statistical analysis: $t = 1{\cdot}8746$; P = NS
Statistical analysis (rheumatoid versus non-rheumatoid):
Episcleritis: $t = 2{\cdot}7092$; P = < 0·005
Scleritis: $t = 1{\cdot}5044$; P = NS

Table IIIc *Sex ratio (rheumatoid episcleritis and rheumatoid scleritis) 46 cases*

Disease	*Cases*	*Females*		*Males*		*Ratio*
		No.	*Per cent*	*No.*	*Per cent*	
Episcleritis	9	9	100	0	—	—
Scleritis	37	25	67·6	12	32·4	2·1/1
		34	73·9	12	26·1	2·8/1

Table IIId *Sex ratio (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases*

Disease	*Cases*	*Females*		*Males*		*Ratio*
		No.	*Per cent*	*No.*	*Per cent*	
Episcleritis	33	16	48·5	17	51·5	1/1·1
Scleritis	18	15	83·3	3	16·7	5/1
		31	60·8	20	39·2	1·6/1

Statistical analysis (female): $\chi^2 = 5{\cdot}9337$; P = < 0·02
Statistical analysis (rheumatoid versus non-rheumatoid (female):
Scleritis: $t = 1{\cdot}5175$; P = NS

Table IIIe *Bilaterality (rheumatoid episcleritis and rheumatoid scleritis)* 46 *cases*

Disease	*Cases*	*Percentage*	*Eye inflammation*			
			Unilateral		*Bilateral*	
			No.	*Per cent*	*No.*	*Per cent*
Episcleritis	9	19·6	5	55·6	4	44·4
Scleritis	37	80·4	12	32·4	25	67·6

Table IIIf *Bilaterality (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Cases*	*Percentage*	*Eye inflammation*			
			Unilateral		*Bilateral*	
			No.	*Per cent*	*No.*	*Per cent*
Episcleritis	33	64·7	13	39·4	20	60·6
Scleritis	18	35·3	11	61·1	7	38·9

showed a similar number of unilateral and bilateral cases (5:4) but rheumatoid scleritis (37 cases) was more commonly bilateral (67·6 per cent). Non-rheumatoid episcleritis (33) was more commonly bilateral (39·4 to 60·6 per cent) and non-rheumatoid scleritis (18) was more often unilateral (61·1 to 38·9 per cent).

PAST MEDICAL HISTORY AND ASSOCIATED DISEASE (Tables IV*a*, *b*)

A breakdown of medical history and associated disease revealed a high incidence of associated abnormality of the cardiovascular and respiratory systems.

Of 30 cases with rheumatoid scleritis (60·0 per cent) in whom electrocardiograms were taken, 18 had ischaemic heart disease. Three further patients complained of angina pectoris but had normal tracings. Six patients with non-rheumatoid episcleritis (21·9 per cent) had electrocardiographic changes and one further patient had a possible pericarditis. Three patients with non-rheumatoid scleritis (16·7 per cent) had ischaemia of the myocardium. There is a significant difference between the incidence of ischaemia in rheumatoid scleritis and that in non-rheumatoid scleritis (P=0·0005). The combined episcleritis/scleritis groups showed a total incidence of myocardial ischaemia in 21 of 37 known cases (56·7 per cent) in comparison with the rheumatoid control group, eight of 20 known cases (40·0 per cent). It is interesting to note that only seven in the episcleritis/scleritis groups did not have an electrocardiogram compared with 16 in the matched control group. Does this reflect the fact that the groups with eye inflammation were more often admitted to the wards, or does it indicate that there was more clinical indication for electrocardiography in the episcleritis/scleritis groups? Certainly clinical examination of the control group had given little evidence of severe cardiovascular disease. The

Table IVa *Past medical history and associated disease (rheumatoid episcleritis and scleritis)* 46 *cases*

Episcleritis (9 cases)			*Scleritis 37 (cases)*		
	No.	*Per cent*		*No.*	*Per cent*
Ischaemic heart disease, 7 cases (2 unknown)	3	42·9	Ischaemic heart disease, 30 cases (7 unknown)	18	60·0
Rheumatic fever	2	22·2	Hypertension, 32 cases (5 unknown)	8	25·0
Hypertension, 7 cases (2 unknown)	1	14·3	Angina pectoris (electrocardiogram normal)	3	8·1
Aortic stenosis	1		Cerebrovascular accident	3	
Cerebrovascular accident	1		Pericarditis	1	2·7
Raynaud's phenomenon	1		Mitral stenosis	1	
Pneumonia	1		Aortic stenosis and incompetence	1	
Pleural effusion	1		Rheumatic fever	1	
Pleurisy	1		Pulmonary embolus	1	
Sinusitis	1		Deep venous thrombosis	1	
Osteoarthritis	1		Pneumonia	5	13·5
Chronic renal disease	1		Pleural effusion	5	
Oral pemphigoid	1		Sinusitis	4	10·8
Gastric ulcer	1		Rheumatoid nodules of lung	3	
Recurrent colitis	1		Tuberculosis of lung	2	
Hemicolectomy	1		Emphysema	2	
Pelvic abscess	1		Asthma	1	
Diabetes	1		Pneumoconiosis	1	
Bilateral otitis media	1		Granulomatous (collagen) disease	1	
			Osteoarthritis	4	
			Dupuytren's contracture	1	
			Psoriatic arthritis	1	
			Duodenal ulcer	4	
			Cholecystectomy	3	
			Hysterectomy	3	
			Diverticulosis	1	
			Adenocarcinoma of bowel	1	
			Appendicectomy	1	
			Prostatectomy	1	
			Prolapsed bowel	1	
			Inguinal hernia	1	
			Hepatitis	1	
			Herpes zoster (trunk)	3	
			Psoriasis	1	
			Rodent ulcer	1	
			Thyrotoxicosis	1	
			Diabetes	1	
			Trigeminal neuralgia	1	
			Pernicious anaemia	1	
			Puerperal fever	1	
			Chronic otitis media	1	

statistically insignificant difference between these two groups might well be misleading.

Excluding respiratory complaints such as bronchitis, emphysema and asthma, pleurisy and rheumatoid pneumonia, pleural effusion, pleurisy and rheumatoid nodules of the lung, both rheumatoid episcleritis and scleritis had a similar incidence of respiratory complications – that is, three of nine cases in episcleritis (33·3 per cent) and 13 of 37 cases in scleritis (35·1 per cent). The incidence of respiratory disease in non-rheumatoid episcleritis and scleritis was much lower; two of 33 cases in episcleritis (6·1 per cent) and one of 18 cases in scleritis (5·6 per cent). The difference in each case is statistically significant (P=0·05 and P=0·025, respectively). The combined rheumatoid episcleritis/scleritis groups gave a total of 16 with rheumatoid respiratory complaints out of 46 cases (34·8 per cent) as compared with five of 45 rheumatoid controls (11·1 per cent). The difference is statistically significant (P=0·01).

Other associated systemic disorders are listed in Tables IV*a*, *b*.

Table IVb *Past medical history and associated disease (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Episcleritis (33 cases)			*Scleritis (18 cases)*		
	No.	*Per cent*		*No.*	*Per cent*
Hypertension, 30 cases (3 unknown)	8	26·7	Hypertension, 16 cases (2 unknown)	4	25·0
Ischaemic heart disease, 32 cases (1 unknown)	6	18·8	Ischaemic heart disease	3	16·7
Valvular heart disease	2	6·1	Rheumatic fever	1	5·5
Rheumatic fever	2		Aortic incompetence	1	
Pericarditis	1	3·0	Migraine	1	
Cerebrovascular accident	1		Sinusitis	5	27·8
Sinusitis	8		Asthma	2	11·1
Pneumonia	2		Tuberculosis of chest	1	
Asthma	2		Bronchitis	1	
Bronchitis	1		Pneumonia	1	
Osteoarthritis	5	15·2	Osteoarthritis	3	16·7
'Rheumatism'	5		'Fibrositis'	2	
'Back trouble'	2		'Slipped disc'	1	
'Fibrositis'	2		'Rheumatism'	1	
'Knee synovitis'	1		Gout	1	
Cervical spondylosis	1		Menopausal haematuria	1	
Paget's disease of spine and ischium	1		Cholecystectomy	2	
Coccygodynia	1		Appendicectomy	2	
Patellar displacement	1		Hysterectomy	2	
Gout	1		Gastritis	1	
Pyelitis	2		'Gastric haemorrhage'	1	
Tuberculosis of kidneys	1		Duodenal ulcer	1	
Hydronephrosis	1		Apical dental abscess	1	
Renal stone	1		Systemic lupus erythematosus	1	
Duodenal ulcer	4	12·1	Erythema nodosa	1	
Hiatus hernia	2		Multiple rodent ulcers	1	
Cholecystitis	1		Jaundice	1	
Appendicectomy	1		Depression	1	
Perianal sinus	1				
Apical dental abscess	1				
Jaundice	1				
Thyroidectomy	1				
Erythema nodosa	2				
Chronic discoid lupus erythematosus	1				
Psoriasis	1				
Pityriasis rosea	1				
Ulcer inguinal region	1				
Acne rosacea	1				
Herpes zoster ophthalmicus	1				
Diabetes	1				
Glandular fever	1				
Puerperal fever	1				

EYE SYMPTOMS (Tables V*a*, *b*)

Redness and ocular pain are by far the commonest complaints in both episcleritis and scleritis. A red eye was referred to only slightly less often in rheu-

Table Va *Eye symptoms (rheumatoid episcleritis and rheumatoid scleritis)* 44 *cases*

Symptoms	*Episcleritis (9 cases)*		*Scleritis (35 cases, 2 unknown)*	
	No.	*Per cent*	*No.*	*Per cent*
Red, inflamed, bloodshot	8	88·9	29	82·9
Ocular pain	3	33·3	16	45·7
Gritty, sandy	2	22·2	11	31·4
Burning	1	11·1	5	14·3
Itching	0		3	8·6
Watering	1		3	
Irritation	1		2	5·7
Photophobia	0		2	
Oedema of lids	0		2	
Headache	0		2	
Discharge, mattering	1		1	2·9
Dryness	1		1	
Blurring of vision	0		1	

Table Vb *Eye symptoms (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Symptoms	*Episcleritis (33 cases)*		*Scleritis (18 cases)*	
	No.	*Per cent*	*No.*	*Per cent*
Red, inflamed, bloodshot	31	93·9	16	88·9
Ocular pain	16	48·5	13	72·2
Gritty, sandy	8	24·2	3	16·7
Headache	4	12·1	1	5·6
Oedema of lids	4		0	
Irritation	3	9·1	3	
Discharge, mattering	3		0	
Burning	2	6·1	2	11·1
Watering	2		0	
Dryness	1	3·0	1	
Blurring of vision	1		1	
Itching	0		1	
Photophobia	0		0	

matoid episcleritis (88·9 per cent) than in non-rheumatoid episcleritis (93·9 per cent), and in rheumatoid scleritis (82·9 per cent) compared with non-rheumatoid scleritis (88·9 per cent). A greater disparity of complaint was notable with regard to ocular pain in rheumatoid episcleritis (33·3 per cent) compared with non-rheumatoid episcleritis (48·5 per cent), and in rheumatoid scleritis (45·7 per cent) compared with non-rheumatoid scleritis (72·2 per cent). The lower incidence of complaint by rheumatoid patients probably reflects the measure of discomfort they experience elsewhere.

LENGTH OF HISTORY OF EYE INFLAMMATION (Tables VI*a*, *b*)

Figures giving the duration of ocular inflammation must be interpreted cautiously, as it is impossible to know whether the inflammation is truly quiescent. However, in each of the four groups of patients the mean duration (with a large standard deviation in each case) showed no significant difference. It was interesting to note that the mean duration of ocular inflammation in the rheumatoid patients was shorter than that in the non-rheumatoid patients; 36·2 months (rheumatoid episcleritis) and 35·0 months (rheumatoid scleritis) compared with 42·4 months (non-rheumatoid episcleritis) and 48·9 months (non-rheumatoid scleritis). There was a wide range in each group, from a few days or weeks to 23½ years.

Table VIa *Length of history of eye inflammation (rheumatoid episcleritis and rheumatoid scleritis)* 40 *cases*

Disease	*Cases*	*Range*	*Mean (months)*	*SD*	*SEM*
Episcleritis	8 (1 unknown)	3 days/ 15 years	36·2	±60·0	±21·2
Scleritis	32 (5 unknown)	1 week/ 20 years	35·0	±54·0	±9·6

Statistical analysis: $t=0·0534$; P=NS

Table VIb *Length of history of eye inflammation (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 49 *cases*

Disease	*Cases*	*Range*	*Mean (months)*	*SD*	*SEM*
Episcleritis	31 (2 unknown)	4 weeks/ 23½ years	42·4	±74·2	±13·3
Scleritis	18	7 weeks/ 20 years	48·9	±74·2	±17·5

Statistical analysis: $t=0·2938$; P=NS
Statistical analysis (rheumatoid versus non-rheumatoid):
Episcleritis: $t=0·1139$; P=NS
Scleritis: $t=0·5713$; P=NS

VISUAL ACUITY (Table VII)

Visual acuity was recorded in the Tennent Institute of Ophthalmology but it was not recorded routinely in patients seen at the Centre for Rheumatic Diseases. An arbitrary dividing line of visual acuity of 6/12 (Snellen), or worse, provided a parameter for the level of visual acuity achieved by each patient. Of the total of 56 eyes with episcleritis, eight eyes (14·3 per cent) had a visual acuity of 6/12 or worse, and of the 41 eyes with scleritis, 15 (36·6 per cent) had a visual acuity of 6/12 or worse. The difference between these two groups is statistically significant (P=0·025). It must be emphasized that refraction was not done as a routine in these cases and that the difference is based on the patient's best visual acuity either with distance glasses or without.

Table VII *Visual acuity (Tennent Institute of Ophthalmology)* 62 *cases*

Disease	*Eyes (total no.)*	*No. of eyes with visual acuity* <6/9	*Percentage*
Episcleritis	56	8	14·3
Scleritis	41	15	36·6

Statistical analysis (episcleritis versus scleritis):
$\chi^2=6·5070$; P= <0·025

TYPE OF INFLAMMATION (Tables VIII*a*, *b*)

All nine cases of rheumatoid episcleritis were of the 'simple' variety. Nodular episcleritis was noted in six cases (18·2 per cent) of the patients with non-rheumatoid inflammation (Fig. 1) and simple episcleritis was recorded in 27 (81·8 per cent). Diffuse scleritis (Fig. 2) was more common in rheumatoid scleritis (83·3 per cent) and non-rheumatoid scleritis (61·1 per cent). A nodular scleritis was slightly less common in rheumatoid scleritis (16·7 per cent) as compared with non-rheumatoid scleritis (33·3 per cent). One case of non-rheumatoid necrotizing scleritis (Fig. 3) presented in a patient who had developed gout some months earlier, but the area of necrotic sclera was

Table VIIIa *Type of inflammation (rheumatoid episcleritis and rheumatoid scleritis)* 45 *cases*

Disease	*Cases*		*Per cent*	*Type*		*Per cent*
Episcleritis	9			Nodular	0	
				Simple	9	
Scleritis	36 (1 unknown)			*Nodular	6	16·7
	Anterior	36	100	Diffuse	30	83·3
	Posterior	8	22·2	Necrotizing	0	

*Scleral translucency in 29 cases (80·6 per cent)

Table VIIIb *Type of inflammation (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Cases*			*Per cent*	*Type*		*Per cent*
Episcleritis	33				Nodular	6	18·2
					Simple	27	81·8
Scleritis	18				Nodular	6	33·3
		Anterior	18	100*	Diffuse	11	61·1
		Posterior	1	5·6	Necrotizing	1	5·6

*Scleral translucency in two cases (11·1 per cent)

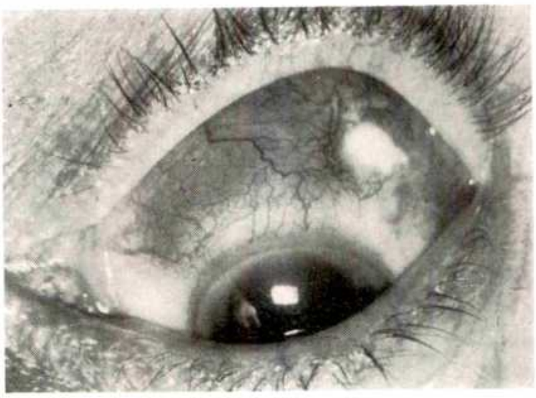


FIG. 3 *Necrotizing scleritis*

probably determined by a subconjunctival injection of methylprednisolone some days previously. Co-existent posterior scleritis was more common in rheumatoid scleritis (22·2 per cent) than in non-rheumatoid scleritis (5·6 per cent). The figure of eight cases in rheumatoid inflammation was a tentative one, based on two cases of choroiditis, one case of retinal detachment, and five cases of extraocular muscle imbalance, suggesting tendon or muscle involvement. These figures do not include patients with macular disturbance which might have been due to other causes. The section on posterior segment abnormality will deal with this in more detail. One of the most interesting findings was the difference between rheumatoid and non-rheumatoid scleritis in the incidence of scleral translucency (Fig. 2). Of 36 cases with rheumatoid scleritis, 29 (80·6 per cent) showed scleral translucency as compared with two of 18 cases with non-rheumatoid scleritis (11·1 per cent).

DISTRIBUTION OF INFLAMMATION (Tables IX*a*, *b*)

The distribution of ocular inflammation in episcleritis is more commonly in the interpalpebral area, suggesting the possibility of external aggravating factors. Scleritis will also affect the superior quadrants of the eye in particular, although less markedly so in non-rheumatoid scleritis. Rheuma-

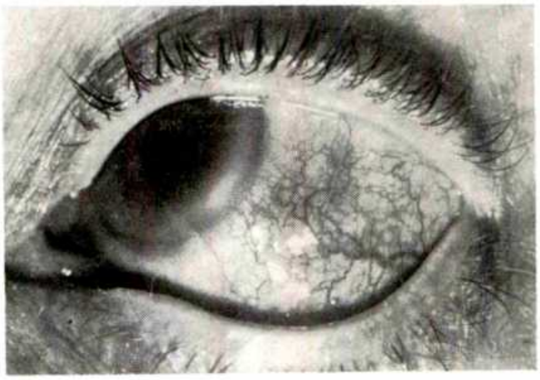


FIG. 1 *Nodular non-rheumatoid episcleritis*

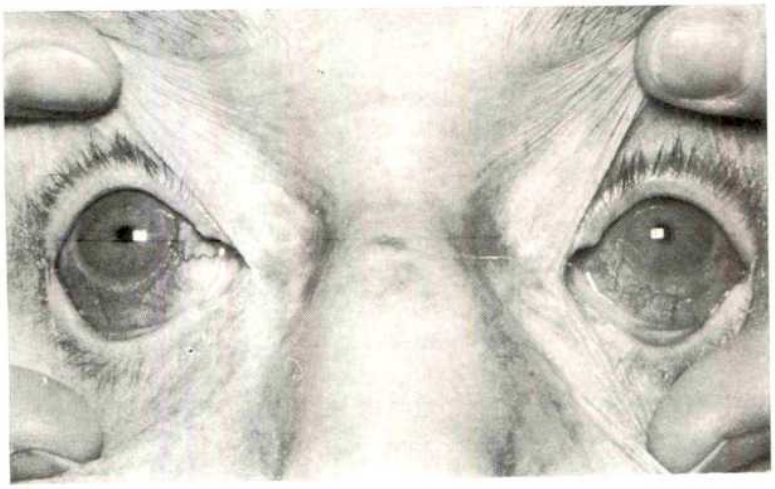
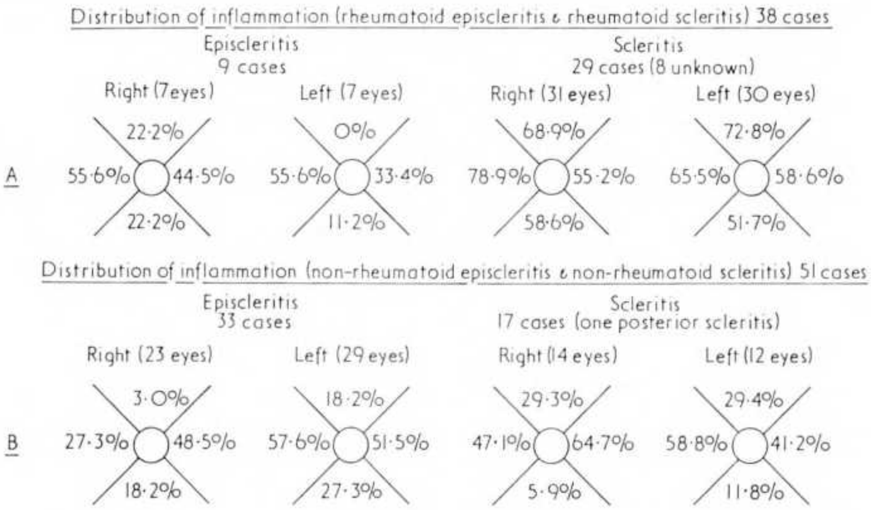


FIG. 2 *Bilateral diffuse scleritis*

Tables IXa, b *Distribution of inflammation*



toid scleritis has a fairly even distribution affecting all quadrants of the anterior sclera.

CORNEAL COMPLICATIONS (Tables X*a*, *b*)

An unexpected finding among the rheumatoid patients was a higher percentage of corneal complications in episcleritis (69·2 per cent) compared with scleritis (43·5 per cent). The small number of 13 eyes with episcleritis, however, may have given an inaccurate picture when one considers the anatomy of the structures involved. The difference is not statistically significant. Non-rheumatoid inflammation showed a lower percentage of corneal involvement in episcleritis (18·9 per cent) than in scleritis (28·0 per cent) although the difference was not statistically significant. Corneal complications showed a higher incidence in rheumatoid as compared with non-rheumatoid disease, which was statistically significant for episcleritis ($P = 0{\cdot}0005$) but not for scleritis.

The predominant corneal complication is a sclerosing keratitis which is usually localized at the site nearest to the inflamed sclera or episclera. Occasionally, in diffuse inflammation, the condition is annular (Fig. 4). The scar of sclerosing keratitis is permanent but in itself has little effect on visual acuity. However, of 10 patients with annular sclerosing keratitis in whom visual acuity was assessed, six (60·0 per cent) had markedly reduced vision due to lens changes.

Limbal guttering occurred in one eye with rheu-

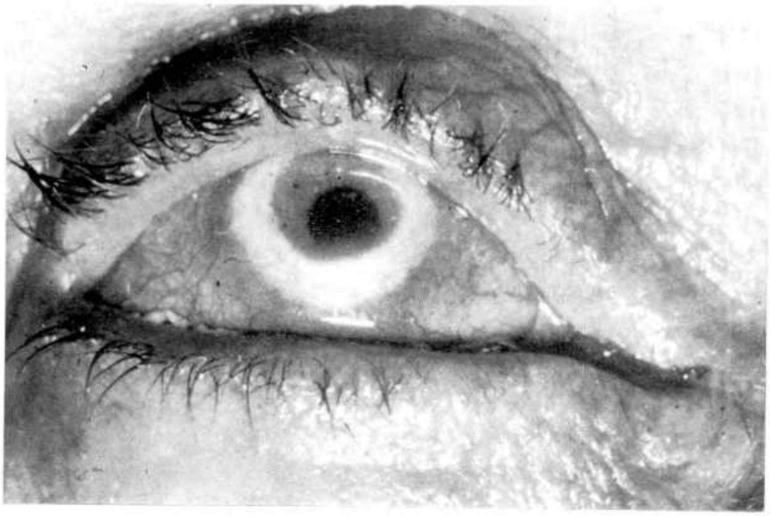


FIG. 4 *Annular sclerosing keratitis in a patient with non-rheumatoid scleritis*

Table Xa *Corneal complications (rheumatoid episcleritis and rheumatoid scleritis)* 46 *cases*

Disease	*Eyes (no.)*	*Eye inflammation*				
		Unilateral	*Cases (no.)*	*Bilateral*	*Cases (no.)*	*Percentage*
Episcleritis	13	Localized stromal	1*	Localized sclerosing	3	69·2
		Localized sclerosing	1			
		Annular sclerosing	1			
Scleritis	62	Localized sclerosing	2	Localized sclerosing	6	43·5
		Annular sclerosing	1	Annular sclerosing	4	
		Keratolysis	1	Grossly degenerate blind	1	
				Localized sclerosing	1*	

Three eyes with scleritis (4·9 per cent) and one with episcleritis (7·6 per cent) developed a limbal gutter at the site of sclerosing keratitis
Statistical analysis: $\chi^2 = 2{\cdot}8399$; P = NS
In all unilateral cases and one bilateral case (marked with asterisk) only one eye was affected

Table Xb *Corneal complications (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Eyes (no.)*	*Eye inflammation*				
		Unilateral	*Cases (no.)*	*Bilateral*	*Cases (no.)*	*Percentage*
Episcleritis	53			Localized sclerosing	2*	18·9
				Localized sclerosing	2	
				Annular sclerosing	1*	
				Limbal guttering	1	
				Band keratopathy	1	
Scleritis	25	Localized sclerosing	3	Annular sclerosing	2*	28·0

Statistical analysis: $\chi^2 = 0{\cdot}8311$; P = NS
Statistical analysis (rheumatoid versus non-rheumatoid):
Episcleritis: $\varkappa^2 = 12{\cdot}9161$; P = < 0·0005
Scleritis: $\varkappa^2 = 1{\cdot}8091$; P = NS
*Both eyes were affected

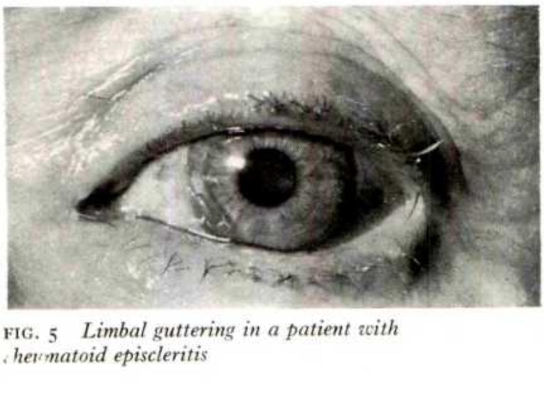


FIG. 5 *Limbal guttering in a patient with rheumatoid episcleritis*

matoid episcleritis, three eyes with rheumatoid scleritis (Fig. 5), and one eye with non-rheumatoid episcleritis. Apart from the last case, each occurred at the site of an area of sclerosing keratitis. A localized stromal keratitis occurred deep in the midstroma in one patient with rheumatoid episcleritis. One patient with rheumatoid scleritis had a perforating keratolysis, which is the corneal counterpart of a perforating scleritis.

ANTERIOR UVEITIS (Tables XI*a*, *b*)

The percentage of eyes with active uveitis or evidence of old uveitis was slightly lower in rheumatoid episcleritis (23·1 per cent) compared with rheumatoid scleritis (28·3 per cent). The difference is not statistically significant. A similar picture emerged in non-rheumatoid episcleritis (17·0 per cent) and non-rheumatoid scleritis (20·0 per cent). Posterior synechiae suggesting a more active and plastic type of uveitis were found in seven of 17 eyes with rheumatoid scleritis (41·2 per cent) as compared with one eye with posterior synechiae associated with non-rheumatoid scleritis (20·0 per cent).

CATARACT (Table XII)

The findings as regards the development of cataract in patients with rheumatoid scleritis who had

Table XIa *Anterior uveitis (rheumatoid episcleritis and rheumatoid scleritis)* 45 *cases*

Disease	*Eyes (no.)*	*Eye inflammation*				
		Unilateral		*Bilateral*		*Percentage*
		Affected eyes	*Cases (no.)*	*Affected eyes*	*Cases (no.)*	
Episcleritis	13	—		2*	1	23·1
				1	1	
Scleritis	60 (2 unknown)	1	1	2	6	28·3
				1	4	

Statistical analysis: $\chi^2 = 0{\cdot}1484$; P = NS

Table XIb *Anterior uveitis (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Eyes (no.)*	*Eye inflammation*				
		Unilateral		*Bilateral*		*Percentage*
		Affected eyes	*Cases (no.)*	*Affected eyes*	*Cases (no.)*	
Episcleritis	53	1	3	2	2	17·0
				1	2	
Scleritis	25	1	4	1	1	20·0

Statistical analysis: $\chi^2 = 0{\cdot}1051$; P = NS
Statistical analysis (rheumatoid versus non-rheumatoid):
Episcleritis: $\chi^2 = 0{\cdot}2608$; P = NS
Scleritis: $\chi^2 = 0{\cdot}6388$; P = NS

Table XII *Posterior subcapsular cataract (PSC) in patients receiving systemic corticosteroids*

Rheumatoid scleritis	*Cases (no.)*	*Mean age ± SD*	*Sex ratio F/M*	*PSC*	*Percentage*
Patients	25	55·89 ± 12·99	3·5/1	9	36·0
'Control' group	148	52·5 ± 11·5	9·6/1	17	11·5

Statistical analysis: $\chi^2 = 10{\cdot}0639$; $P = < 0{\cdot}005$

received treatment with systemic corticosteroids are of particular interest. The incidence of posterior subcapsular cataract in patients with rheumatoid scleritis who had been treated with systemic corticosteroids was high (36·0 per cent). Nine of 25 patients who had received treatment with systemic corticosteroids had developed posterior subcapsular cataract. There were three further patients who had advanced cataract, two of whom had bilateral cataract (one had one aphakic eye), but these are not included for the purposes of statistical analysis. A previous study involving two of us (JW and DDMM), of the incidence of steroid-induced cataract in patients with rheumatoid arthritis, found that 17 of 148 patients with rheumatoid arthritis (11·5 per cent) who had received systemic corticosteroids had posterior subcapsular cataracts. These patients also attended the Centre for Rheumatic Diseases, Glasgow. Comparison of the incidence of posterior subcapsular cataract in rheumatoid scleritis (36·0 per cent) with posterior subcapsular cataract in patients with rheumatoid arthritis without scleritis (11·5 per cent), both groups receiving systemic corticosteroid treatment, is statistically significant (P=0·005).

Only three other patients in the study had the characteristic form of cataract. One patient with rheumatoid episcleritis had bilateral posterior subcapsular cataract and had been treated with systemic corticosteroids for an uncertain length of time. It is interesting that of 51 patients with non-rheumatoid episcleritis or scleritis, two patients developed posterior subcapsular cataract, and these were the only two patients of the non-rheumatoid group who were receiving systemic corticosteroid treatment.

POSTERIOR SEGMENT ABNORMALITY (Tables XIIIa, *b*)

No patient with rheumatoid episcleritis had abnormality of the posterior segment of the eye. However, the percentage of abnormal features in association with rheumatoid scleritis was 29·1 per cent. The commonest abnormality was a macular disturbance in 11 eyes (20·0 per cent), although three of these eyes were myopic, and this might have affected their macular state. The origin of macular disturbance is difficult to determine in these cases, and the results need to be viewed with caution. Many of the rheumatoid patients received a number of different antirheumatic drugs which might have disturbed the retinal picture. However, macular disturbance is a recognized complication of scleritis (Watson and Lobascher, 1965). Two eyes showed old foci of choroiditis and one eye, in a patient now deceased, optic atrophy of obscure origin, although the eye had been grossly inflamed and suffered a subsequent perforating keratolysis. It was interesting to find oedema of the optic nerve head in one case, suggesting a possible ischaemic optic neuropathy. One patient had an old detached retina.

There was an area of old choroiditis in one case diagnosed as non-rheumatoid episcleritis (1·9 per cent of 52 eyes). Two eyes with non-rheumatoid scleritis had a possibly significant abnormality of the posterior pole (8·0 per cent of 25 eyes); in both cases these were areas of macular disturbance.

There was a marked difference in the incidence of abnormality between rheumatoid episcleritis and scleritis. The significant difference between posterior segment complications in rheumatoid scleritis and non-rheumatoid scleritis (P=0·05) may reflect more severe disease in the rheumatoid patient.

INTRAOCULAR PRESSURE (Tables XIVa, *b*)

One patient with rheumatoid episcleritis had bilateral raised intraocular pressure, but this was

Table XIIIa *Posterior segment abnormality (rheumatoid episcleritis and rheumatoid scleritis) 42 cases*

Episcleritis 9 eyes (4 unknown)	*Scleritis 55 eyes (7 unknown)**		*Percentage*
—	Macular disturbance	11	20·0†
	Old choroiditis	2	4·2
	Optic atrophy	1	2·1
	Oedema of optic nerve head	1	
	Old detached retina	1	
			29·1

*Two cases were obscured by cataract
†Three eyes were myopic

Table XIIIb *Posterior segment abnormality (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases*

Episcleritis 52 eyes (1 unknown)		*Percentage**	*Scleritis 25 eyes*		*Percentage*
Old choroiditis	1	1·9	Macular disturbance	2	8·0

*One case obscured by band keratopathy
Statistical analysis: $\chi^2 = 1{\cdot}6651$; P=NS
Statistical analysis (rheumatoid versus non-rheumatoid):
Scleritis: $\chi^2 = 4{\cdot}3844$; $P = < 0{\cdot}05$

Table XIVa *Raised intraocular pressure* (rheumatoid episcleritis and rheumatoid scleritis)* 37 *cases*

Disease	*Eyes (no.)*	*Eye inflammation*						*Percentage*
		Unilateral			*Bilateral*			
		Cases	*Eyes affected*	*IOP mmHg*	*Cases*	*Eyes affected*	*IOP mmHg*	
Episcleritis	9 (4 unknown)	1	2	26 +25	—			—
Scleritis	48 (14 unknown)	1	1	22	2	2	29 +32 26 +23	18·7
					4	1	22	
					Absolute glaucoma		22 32	

*The highest reading recorded is given in each case
†A case of closed-angle glaucoma not considered as positive as the raised pressure was not due to inflammation

Table XIVb *Raised intraocular pressure (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Eyes (no.)*	*Eye inflammation*						*Percentage*
		Unilateral			*Bilateral*			
		Cases	*Eyes affected*	*IOP mmHg*	*Cases*	*Eyes affected*	*IOP mmHg*	
Episcleritis	53	—			1	1	22	1·9
Scleritis	25	3	1	26 30 38	—			12·0
		2	2*	30 +28 30 +34				

*Both these cases, although unilateral cases of scleritis, received topical steroids to both eyes. On withdrawing topical steroids all four eyes reverted to normal intraocular pressures. They are considered cases of steroid-induced glaucoma and not primarily due to inflammation.
Statistical analysis (rheumatoid versus non-rheumatoid): Scleritis, $\chi^2 = 0{\cdot}5453$; P = NS

due to closed-angle glaucoma and the condition settled with bilateral peripheral iridectomies. No other patient with rheumatoid episcleritis had raised intraocular pressure. Nine eyes with rheumatoid scleritis (18·7 per cent) had raised intraocular pressure; in two cases there was absolute glaucoma. Four eyes had levels recorded by applanation tonometry at or between 22 and 26 mmHg. One eye, with a reading at 22 mmHg, was a case of old 'burnt out' absolute glaucoma. One eye had a reading at 29 mmHg, one at 30 mmHg, and two at 32 mmHg.

Only one patient with non-rheumatoid episcleritis had one eye with a tension fractionally above normal at 22 mmHg, a percentage of 1·9 per cent. Seven eyes with non-rheumatoid scleritis had raised levels but in two cases (four eyes) the level of pressure fell from 30 mmHg (right) + 28 mmHg (left) and 30 mmHg (right) + 34 mmHg (left) to within normal limits on withdrawing topical steroid treatment. It is considered that these were cases of steroid-induced glaucoma. The remaining three cases (12·0 per cent) include one patient in whom the intraocular pressure was 38 mmHg. In each case the highest reading recorded is given. Only one patient, a woman with unilateral rheumatoid scleritis, required a drainage procedure to control her intraocular pressure. There was no flare-up of her scleritis. One patient with a pressure at 22 mmHg in one eye is still receiving miotic treatment. The intraocular pressure of the remaining patients all settled coincident with the quietening of their inflammation, including those patients in whom pressures were recorded in the 30–38 mmHg range.

OCULAR MOVEMENTS (Tables XV*a*, *b*)

No patient with rheumatoid episcleritis had evidence of muscle imbalance. Eight eyes with rheumatoid scleritis (12·9 per cent) showed limitation of movement of one extraocular muscle or more. Two cases, however, were based on a history of transient diplopia, suggesting tendon or muscle involvement consistent with the site of scleral inflammation. The limitation of movement in the remaining six cases was substantiated by orthoptic examination.

Three cases of non-rheumatoid episcleritis (5·7 per cent) suggested possible tendon and/or muscle

Table XVa *Ocular movements (rheumatoid episcleritis and rheumatoid scleritis)* 46 *cases*

Disease	*Eyes (no.)*	*Muscle imbalance*	*Percentage*
Episcleritis	13	—	—
Scleritis	62	8*	12·9

*Two cases based on history of transient diplopia

Table XVb *Ocular movement (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Eyes (no.)*	*Muscle imbalance*	*Percentage*
Episcleritis	53	3*	5·7
Scleritis	25	6†	24·0

*All three cases tentatively based on history of transient diplopia
†One case based on a history of intermittent diplopia
Statistical analysis (non-rheumatoid episcleritis versus non-rheumatoid scleritis): $\chi^2=5{\cdot}5976$: $P=<0{\cdot}025$
Statistical analysis (rheumatoid versus non-rheumatoid):
Scleritis: $\chi^2=1{\cdot}6248$; P=NS

inflammation, but the conclusion is tentative. All three cases gave a brief history of diplopia which they associated with an inflamed eye. Six cases with non-rheumatoid scleritis (24·0 per cent) gave evidence of tendon and/or muscle imbalance, one case based on an account of intermittent diplopia and the remaining five cases confirmed by an orthoptic assessment. The difference in incidence between non-rheumatoid episcleritis and non-rheumatoid scleritis is statistically significant ($P=0{\cdot}025$).

One patient, a 34-year-old woman who had non-rheumatoid scleritis presented with a dramatic strabismus. Examination revealed a paresis of the left lateral rectus muscle. This was the third time in three years that she had had an inflamed eye. On the first occasion there had been a paresis of the right medial rectus muscle. A biopsy (1×3 mm) of the middle section of tendon and muscle of the left lateral rectus muscle confirmed the presence of a tenomyositis. Chemosis was characteristic of each episode after a few days of ocular pain, and on each occasion was thought to herald the onset of an orbital cellulitis.

KERATOCONJUNCTIVITIS SICCA (Tables XVI*a*, *b*)

One patient with rheumatoid episcleritis (14·2 per cent) had definite KCS, and four patients with rheumatoid scleritis (12·9 per cent). Of the patients with non-rheumatoid inflammation, four with episcleritis (12·1 per cent), and one with scleritis (5·6 per cent) had KCS.

There were three further cases of possible KCS. One case was associated with rheumatoid episcleritis and two cases with rheumatoid scleritis. In each the Schirmer I tear test was markedly reduced. All three patients had died before complete examination could be carried out and no Schirmer II test or rose bengal staining had been done.

SJÖGREN'S SYNDROME

Sjögren's syndrome is defined as a triad of features; KCS, xerostomia (with or without salivary gland swelling), and a connective-tissue disease. The presence of either KCS or xerostomia with a systemic disorder is accepted as sufficient (Bloch, Buchanan, Wohl, and Bunim, 1965).

Only two of the 37 cases of rheumatoid scleritis exhibited the triad of dry eyes, dry mouth, and a connective-tissue disorder (in this case rheumatoid arthritis). No case of rheumatoid episcleritis had the triad of features of Sjögren's syndrome. However, two further cases of rheumatoid scleritis and one case of rheumatoid episcleritis had KCS associated with the systemic disease. Eight further cases of rheumatoid scleritis and two cases of rheumatoid episcleritis also had xerostomia with rheumatoid arthritis. This means that the total incidence of Sjögren's syndrome, according to the criteria given, is 12 of 37 cases of rheumatoid scleritis (32·4 per cent) and three of nine cases of rheumatoid episcleritis (33·3 per cent).

SICCA SYNDROME

One patient with non-rheumatoid episcleritis (3·0 per cent) had dry eyes combined with a dry

Table XVIa *Keratoconjunctivitis sicca (rheumatoid episcleritis and rheumatoid scleritis)* 42 *cases*

Disease	*Cases (no.)*	*No. of KCS cases*	*Percentage*
Episcleritis	8 (1 unknown)*	1	14·2
Scleritis	34 (3 unknown)†	4	12·9

*The 'unknown' case had a markedly reduced Schirmer I test
†Two 'unknown' cases had markedly reduced Schirmer I tests (one case is included as a positive KCS because of a reduced Schirmer I test with widespread rose bengal staining)
Statistical analysis: $\chi^2=0{\cdot}0096$; P=NS

Table XVIb *Keratoconjunctivitis sicca (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Disease	*Cases (no.)*	*No. of KCS cases*	*Percentage*
Episcleritis	33	4	12·1
Scleritis	18	1	5·6

Statistical analysis: $\chi^2=0{\cdot}5678$; P=NS
Statistical analysis (rheumatoid versus non-rheumatoid):
Episcleritis: $\chi^2=0{\cdot}0247$; P=NS
Scleritis: $\chi^2=0{\cdot}6710$; P=NS

Table XVII *Articular features of patients with rheumatoid episcleritis and rheumatoid scleritis*

Features	*Rheumatoid episcleritis/scleritis*					*Rheumatoid controls*					*P value*
	No. of cases	*Range (years)*	*Mean (years)*	*SD*	*SEM*	*No. of cases*	*Range (years)*	*Mean (years)*	*SD*	*SEM*	
Duration of rheumatoid arthritis	46	0·5–50	14·5	±12·9	±1·9	46	0·17–48	9·2	±10·2	±1·5	<0·05
Functional class	45	1–4	2·7	±0·9	±0·14	46	1–4	2·28	±0·78	±0·11	NS
Articular index	43	0–78	23·1	±20·0	±3·1	41	0–53	19·0	±12·9	±2·0	NS
X-ray stage	36	1–4	2·97	±0·61	±0·1	38	1–4	2·42	±1·03	±0·17	<0·01

NS = Not significant

mouth, features of the sicca syndrome, in which the dryness of mucous membranes is not associated with a connective-tissue disorder.

RHEUMATOLOGY

The following data refer to those patients with rheumatoid episcleritis or rheumatoid scleritis and compare them with a group of rheumatoid controls, matched for age and sex – that is, patients with rheumatoid arthritis but with no evidence of episcleral or scleral inflammation. For the purposes of this paper, as regards the articular and extra-articular features of rheumatoid disease, the patients with rheumatoid episcleritis and scleritis are combined as one group and compared with the rheumatoid control group.

DURATION OF RHEUMATOID ARTHRITIS; FUNCTIONAL CLASS; ARTICULAR INDEX, AND X-RAY STAGE (Table XVII)

The range of duration was huge in both rheumatoid episcleritis/scleritis and in rheumatoid controls, from a few months to 50 years. However, episcleritis and scleritis occurred in patients with longer-standing rheumatoid arthritis (mean values 14·5 years compared with 9·2 years). The difference is statistically significant (P=0·05).

The functional class measures in four grades of increasing severity the degree of functional incapacity due to arthritis. The study of functional incapacity was the only investigation in which the rheumatoid control group showed a more severe degree of abnormality compared with the rheumatoid episcleritis/scleritis group. The mean value for 45 known cases of rheumatoid episcleritis/scleritis was 2·17 and for 46 cases in the rheumatoid control group was 2·28.

The articular index records the number of involved joints and the severity of their involvement as judged by tenderness to pressure over the joint margin. The matched group of rheumatoid controls had a mean value of 19. The difference between the control group and the combined rheumatoid episcleritis/scleritis group (mean value: 23·1) was not statistically significant.

The *x*-ray stage indicates radiologically the degree of bone and joint involvement categorized in four stages of increasing severity. Comparison of the rheumatoid episcleritis/scleritis group (mean value: 2·97) and the group of rheumatoid controls (mean value: 2·42) indicated that episcleritis and scleritis occurred in a group with more severe erosive arthritis. The difference is statistically significant (P=0·01).

SUBCUTANEOUS NODULES; PERIPHERAL NEUROPATHY; SKIN ULCERS; SKIN BRUISING; SKIN ATROPHY; AMYLOID; TENDON RUPTURE AND SPLENOMEGALY (Table XVIII)

Of 46 cases with rheumatoid episcleritis or scleritis 23 had subcutaneous granulomatous nodules

Table XVIII *Extra-articular features in patients with rheumatoid episcleritis and rheumatoid scleritis*

Extra-articular features	*Rheumatoid episcleritis/scleritis*			*Rheumatoid controls*			*P value*
	No. of cases	*No. of cases positive*	*Per cent*	*No. of cases*	*No. of cases positive*	*Per cent*	
Subcutaneous nodules	46	23	50·0	46	11	23·9	<0·01
Peripheral neuropathy	45	3	8·9	46	1	2·2	NS
Skin ulcers	45	6	13·3	46	2	4·4	NS
bruising	46	11	23·9	46	5	10·9	NS
atrophy	46	16	34·8	46	5	10·9	<0·01
Amyloid	46	2	4·4	46	0	—	—
Splenomegaly	46	5	10·9	46	1	2·2	NS
Tendon rupture	46	0	—	46	0	—	—

(50·0 per cent). Comparison with the incidence in the rheumatoid control group (23·9 per cent) showed a statistically significant difference (P=0·01).

Three of 45 known cases of rheumatoid episcleritis or scleritis (8·9 per cent) revealed a high incidence of peripheral neuropathy as compared with only one case in the rheumatoid control group (2·2 per cent). However, the difference is not statistically significant. Two of the patients with rheumatoid episcleritis/scleritis had received treatment with systemic corticosteroids and two had been given gold therapy (one patient had received both). Either of these treatments could have produced neuropathy. The patient in the rheumatoid control group had not received systemic treatment with corticosteroids or gold.

Six of 45 known cases with rheumatoid episcleritis or scleritis (13·3 per cent) had skin ulceration as compared with two of 46 cases in the rheumatoid control group (4·4 per cent). The difference is not statistically significant for these numbers. Three of the patients with rheumatoid episcleritis or scleritis had received treatment with systemic corticosteroids and both patients in the rheumatoid control group had received similar medication.

Skin bruising occurred more often in patients with rheumatoid episcleritis or scleritis (11 cases; 23·9 per cent) as compared with the rheumatoid controls (5 cases; 10·9 per cent). The difference for these numbers is not statistically significant. Ten of the patients in the rheumatoid episcleritis/scleritis group had received treatment with systemic corticosteroids and four of the five positive cases in the rheumatoid control group had been similarly treated.

Skin atrophy was found in 16 patients in the rheumatoid episcleritis/scleritis group (34·8 per cent) as compared with five patients in the rheumatoid control group (10·9 per cent); this is statistically significant (P=0·01). Ten of the patients in the rheumatoid episcleritis/scleritis group and five in the rheumatoid control group had been given systemic corticosteroid treatment.

There were two men considered as having secondary amyloidosis; both had bilateral rheumatoid scleritis. One case was confirmed by liver biopsy. No case of amyloidosis was confirmed in the group of rheumatoid controls.

No patient with rheumatoid episcleritis/scleritis and none of the rheumatoid control group suffered tendon rupture.

The incidence of splenomegaly in the rheumatoid episcleritis/scleritis group was five of 46 cases (10·9 per cent). Only one patient of 46 rheumatoid controls (2·2 per cent) had a palpable spleen. The difference for these numbers is not statistically significant.

Laboratory investigations

The following data record information found in six groups of patients; patients with rheumatoid episcleritis and rheumatoid scleritis, non-rheumatoid episcleritis and non-rheumatoid scleritis, and patients with rheumatoid episcleritis and scleritis combined as one group for comparison with the rheumatoid control group.

HAEMOGLOBIN; ERYTHROCYTE SEDIMENTATION RATE (ESR); ALBUMIN/GLOBULIN RATIO; ALKALINE PHOSPHATASE; URIC ACID; SERUM GLUTAMIC OXALOACETIC TRANSAMINASE (SGOT), and SERUM GLUTAMIC PYRUVIC TRANSAMINASE (SGPT) (Tables XIX*a*, *b*, *c*)

For the purposes of comparison haemoglobin results for both men and women are grouped together. In patients with rheumatoid episcleritis the mean value was 87·6 per cent but in those with rheumatoid scleritis it was 83·4 per cent. The mean haemoglobin value for patients with non-

Table XIXa *Laboratory investigations in patients with rheumatoid episcleritis and rheumatoid scleritis*

Laboratory investigation	*Rheumatoid episcleritis*				*Rheumatoid scleritis*				P *value*
	No. of cases	*Mean*	*SD*	*SEM*	*No. of cases*	*Mean*	*SD*	*SEM*	
Haemoglobin ESR	9	87·6 per cent	±15·4	±5·1	37	83·4 per cent	±18·2	±3·0	NS
	7	74·4 mm/1st h (Westergren)	±37·9	±14·3	30	65·3 mm/1st h (Westergren)	±36·1	±6·6	NS
Albumin/globulin ratio	9	0·88	±0·37	±0·12	37	1·03	±0·41	±0·07	NS
Alkaline phosphatase	9	12·07 KA units	±4·73	±1·58	37	14·68 KA units	±12·73	±2·09	NS
Uric acid	8	4·6 mg/100 ml	±1·66	±0·59	35	4·88 mg/100 ml	±1·47	±0·25	NS
SGOT	8	17·88 IU/l	±8·17	±2·89	30	29·33 IU/l	±43·23	±7·89	NS
SGPT	8	15·88 IU/l	±12·86	±4·55	30	23·87 IU/l	±36·3	±6·63	NS

Normal values: haemoglobin 90–125 per cent male, 80–110 per cent female; ESR 5–12 mm/1st h male, 0–7 mm female; A/G ratio 1·03–2·36 g/100 ml; alkaline phosphatase 5–15 KA units; uric acid 2·2–7·2 mg/100 ml male, 0·5–5·7 mg/100 ml female; SGOT 11–35 IU/l; SGPT 4–28 IU/l

Table XIXb *Laboratory investigations in patients with non-rheumatoid episcleritis and non-rheumatoid scleritis*

	Non-rheumatoid episcleritis				*Non-rheumatoid scleritis*				
Laboratory investigations	*No. of cases*	*Mean*	*SD*	*SEM*	*No. of cases*	*Mean*	*SD*	*SEM*	P *value*
Haemoglobin	31	99·9 per cent	±9·2	±1·6	18	98·4 per cent	±8·0	±1·9	NS
ESR	27	13·3 mm/1st h (Wintrobe)	±12·8	±2·5	15	19·9 mm/1st h (Wintrobe)	±13·0	±3·4	NS
Albumin/globulin ratio	33	1·75	±0·38	±0·07	18	1·53	±0·33	±0·08	<0·05
Alkaline phosphatase	33	7·36 KA units	±2·61	±0·45	18	8·06 KA units	±3·33	±0·79	NS
Uric acid	33	5·39 mg/100 ml	±1·90	±0·33	18	4·41 mg/100 ml	±1·25	±0·29	NS
SGOT	32	20·56 IU/l	±7·9	±1·4	18	22·67 IU/l	±16·04	±3·78	NS
SGPT	32	19·88 IU/l	±9·13	±1·61	18	19·39 IU/l	±12·7	±2·99	NS

Normal values are given with Table XIXa

Table XIXc *Laboratory investigations in patients with rheumatoid episcleritis and rheumatoid scleritis: comparison with rheumatoid controls*

	Rheumatoid episcleritis/scleritis				*Rheumatoid controls*				
Laboratory investigations	*No. of cases*	*Mean*	*SD*	*SEM*	*No. of cases*	*Mean*	*SD*	*SEM*	P *value*
Haemoglobin	46	84·3 per cent	±17·6	±2·6	45	90·1 per cent	±12·3	±1·83	NS
ESR	37	67·1 mm/1st h (Westergren)	±36·1	±5·9	45	48·4 mm/1st h (Westergren)	±34·1	±5·1	<0·025
Albumin/globulin ratio	46	1·0	±0·4	±0·6	40	1·12	±0·39	±0·06	NS
Alkaline phosphatase	46	14·2 KA units	±11·6	±1·7	41	11·5 KA units	±3·7	±0·58	NS
Uric acid	43	4·8 mg/100 ml	±1·5	±0·23	40	4·36 mg/100 ml	±1·14	±0·18	NS
SGOT	38	26·9 IU/l	±38·7	±6·3	27	14·6 IU/l	±5·1	±1·0	NS
SGPT	38	22·2 IU/l	±32·8	±5·3	23	12·0 IU/l	±5·5	±1·1	NS

Normal values are given with Table XIXa

rheumatoid episcleritis was 99·9 per cent, significantly higher than in those with rheumatoid episcleritis (P=0·005). A similar significant difference was found for patients with non-rheumatoid scleritis, in whom the mean value for haemoglobin was 98·4 per cent, compared with patients with rheumatoid scleritis (P=0·005). Comparison of the rheumatoid episcleritis/scleritis group with rheumatoid controls suggested that the anaemia might be more severe in patients with eye inflammation (84·3 to 90·1 per cent) but the difference is not statistically significant for these numbers.

For the purposes of comparison ESR readings for both men and women are grouped together. The ESR in rheumatoid inflammation was very much higher than that in patients with non-rheumatoid episcleritis or scleritis. Unfortunately the methods differed in the two groups. The Westergren method was used at the Centre for Rheumatic Diseases and the Wintrobe method at the Tennent Institute. There is, however, an obvious difference in severity which does not require exact comparison. The mean value in rheumatoid episcleritis was 74·4 mm/1st hour and in rheumatoid scleritis 65·3 mm/1st hour (Westergren). Patients with non-rheumatoid episcleritis had a mean value of 13·3 mm/1st hour and those with non-rheumatoid scleritis gave a mean value of 19·9 mm/1st hour (Wintrobe). The ESR in rheumatoid episcleritis/scleritis patients was higher than in the rheumatoid control group; mean values were 67·1 mm compared with 48·4 mm. The difference in these values is statistically significant (P=0·025).

The mean value of the albumin/globulin ratio in rheumatoid episcleritis was 0·88 while that for rheumatoid scleritis was 1·03. There was a high percentage of reversed ratios in both rheumatoid episcleritis (66·7 per cent) and scleritis (62·2 per cent). Non-rheumatoid patients with episcleritis showed a mean value of 1·75 and those with scleritis a mean value of 1·53. The difference between these two figures is significant (P=0·05). Neither of the groups with non-rheumatoid inflammation had any patient with a reversed ratio. There was a highly significant difference between rheumatoid and non-rheumatoid episcleritis (P=0·001) and rheumatoid and non-rheumatoid scleritis (P=0·001). The mean value of the albumin/globulin ratio in the rheumatoid episcleritis/scleritis group (1·0) was more abnormal than the group of rheumatoid controls (1·12), but the difference was not statistically significant. Consistent with these findings, the number of patients with a reversed albumin/globulin ratio was greater in the combined episcleritis/scleritis group (63·0 per cent) than in the rheumatoid control group (47·5 per cent).

None of the mean values in all six groups studied is outside the normal range for alkaline phosphatase of 5–15 King Armstrong units, although it is interesting to note that the mean value for rheumatoid scleritis is at the upper limit of normal, and also that 10 of 37 cases with rheumatoid scleritis (27·0 per cent) had raised readings. Further, it is noteworthy that there is a statistically significant difference between the levels for rheumatoid episcleritis and non-rheumatoid episcleritis (P=0·001) and between rheumatoid scleritis and non-rheumatoid scleritis (P=0·05).

As with alkaline phosphatase, none of the mean values for serum uric acid levels in the six groups of patients investigated was outside the normal range.

A similar pattern emerged for SGOT and SGPT, where all mean values recorded were within normal limits.

WASSERMANN REACTION; VDRL SLIDE TEST, AND REITER PROTEIN COMPLEMENT-FIXATION TEST

The following data relate only to those patients with eye inflammation, both rheumatoid and non-rheumatoid. Seven of the patients with rheumatoid episcleritis and 28 of the patients with rheumatoid scleritis had these investigations and no patient gave a positive result. All the patients with non-rheumatoid episcleritis and with non-rheumatoid scleritis gave similarly negative results.

ANTISTREPTOLYSIN-O TITRE (ASO); BRUCELLOSIS AND TOXOPLASMOSIS

The following data relate only to those patients with rheumatoid episcleritis and scleritis, and non-rheumatoid episcleritis and scleritis.

One patient with rheumatoid episcleritis (14·3 per cent) had a raised ASO titre at 724 units and six with rheumatoid scleritis (20·7 per cent) had raised titres at 320 units (2), 400 units (2), 500 units, and 640 units. Three patients with non-rheumatoid episcleritis (9·1 per cent) showed raised ASO titres, two readings at 320 units and one at 1280 units. One case of non-rheumatoid scleritis (5·6 per cent) had a raised titre at 320 units. None of the patients with a raised ASO titre had erythema nodosum.

Only one of 28 patients with rheumatoid scleritis (3·5 per cent) had a tentative positive result for brucellosis. The standard agglutination test gave a titre of 1/80 for *Brucella abortus*, but the Coombs' test was negative. Serum was anti-complementary. One patient with non-rheumatoid episcleritis (3·1 per cent) had a positive titre for *Brucella abortus* at 1/160 in both the standard agglutination and Coombs' test. However, the complement-fixation test was negative.

The only group of patients with a percentage incidence of positive toxoplasmosis dye test titres outside the normal adult range, approximately 30–40 per cent (Ludlam, 1972), was the very small group of seven cases with rheumatoid episcleritis in which the percentage was 71·4 per cent (Tables XX*a*, *b*). It is interesting to note that 8·6 per cent of the patients with rheumatoid episcleritis or rheumatoid scleritis had a titre of 1/256 or more. The group with non-rheumatoid episcleritis and non-rheumatoid scleritis showed only one in the same range (1/1024), 2·0 per cent. It is probable that in the normal adult population the incidence of antibodies at a titre of 1/256 is not more than 1·0 per cent (Beattie, 1958; Ludlam and Beattie, 1963).

AUTOANTIBODIES (Tables XXI*a*, *b*)

The following results refer only to those patients with rheumatoid and non-rheumatoid eye inflam-

Table XXa *Toxoplasma dye test titres in* 35 *cases* (*rheumatoid episcleritis and rheumatoid scleritis*)

Disease	*Cases*	< 1/8	+1/8	+1/16	+1/32	+1/64	+1/128	+1/256	+1/512	+1/1024
Episcleritis	7 (2 unknown)	2	—	1	2	—	1	—	—	1
				Total+	5 (71·4 per cent)					
Scleritis	28 (9 unknown)	15	3	1	6	—	1	1	1	—
				Total+	13 (46·4 per cent)					

Table XXb *Toxoplasmosis* (*non-rheumatoid episcleritis and non-rheumatoid scleritis*) 51 *cases*

Disease	*Cases*	< 1/8	+1/8	+1/16	+1/32	+1/64	+1/128	+1/256	+1/512	+1/1024
Episcleritis	33	17	5	—	8	2	1	—	—	—
				Total+	16 (48·5 per cent)					
Scleritis	18	12	—	1	1	3	—	—	—	1
				Total+	5 (27·8 per cent)					

Table XXIa *Autoantibodies (rheumatoid episcleritis and rheumatoid scleritis)* 46 *cases*

Autoantibody	*Cases (no.)*	*Episcleritis (9 cases)* +	*Weakly* +	*Percentage*
Rheumatoid latex	9	9	0	100
Antinuclear factor	9	2	0	22·2
Thyroglobulin TRC	9	0	0	—
Thyroid microsomal	9	1	0	11·1
Smooth muscle	8 (1 unknown)	1	0	12·5
Salivary duct	9	4	0	44·4
Gastric parietal cell	9	3	0	33·3
Mitochondrial	8 (1 unknown)	0	0	—
		Scleritis (37 cases)		
Rheumatoid latex	37	35	1	97·3*
Antinuclear factor	37	8	1	24·3
Thyroglobulin TRC	37	3	0	8·1
Thyroid microsomal	37	4	2	16·2
Smooth muscle	34 (3 unknown)	2	6	23·5
Salivary duct	35 (2 unknown)	5	5	28·6
Gastric parietal cell	37	5	1	16·2
Mitochondrial	34 (3 unknown)	0	0	—

*One case is included in which the Rose-Waaler test was used

Table XXIb *Autoantibodies (non-rheumatoid episcleritis and non-rheumatoid scleritis)* 51 *cases*

Autoantibody	*Episcleritis (33 cases)* +	*Weakly* +	*Percentage*
Rheumatoid latex	0	1	3·0
Antinuclear factor	1	2	9·1
Thyroglobulin TRC	0	1	3·0
Thyroid microsomal	3	1	12·1
Smooth muscle	0	0	—
Salivary duct	0	0	—
Gastric parietal cell	1	4	15·2
Mitochondrial	0	0	—
	Scleritis (18 cases)		
Rheumatoid latex	0	6	33·3
Antinuclear factor	4	2	33·3
Thyroglobulin TRC	0	0	—
Thyroid microsomal	1	0	5·6
Smooth muscle	1	1	11·1
Salivary duct	0	0	—
Gastric parietal cell	2	0	11·1
Mitochondrial	0	0	—

mation. Apart from the relatively high incidence of salivary duct antibody in the small group with rheumatoid episcleritis, where a positive result was given in four of nine cases (44·4 per cent), and an apparently high incidence of smooth-muscle antibody in rheumatoid scleritis, where eight of 34 cases were positive (23·5 per cent) (although six of these were only weakly positive) the positive autoantibodies listed in Table XXI*a* in patients with rheumatoid episcleritis and rheumatoid scleritis is generally in the range expected for patients with rheumatoid arthritis (see Discussion). The possibly significant finding in the non-rheumatoid patients is the high incidence of a weakly positive rheumatoid factor in patients with non-rheumatoid scleritis, six of 18 cases (33·3 per cent). Also, six patients had a positive antinuclear factor (33·3 per cent); in two of them this was weakly positive. Three patients had a positive rheumatoid factor together with a positive antinuclear factor. The remaining autoantibody investigations in the non-rheumatoid patients were in the range accepted for a general population (see Discussion).

R_3 TITRE (Table XXII)

Sixteen of the rheumatoid episcleritis/scleritis group (42·1 per cent) had titres of 1/512 or higher compared with eight of the rheumatoid controls (21·6 per cent). The difference was just outside significance for these numbers ($\chi^2=3{\cdot}6148$).

1C/1A GLOBULIN (HUMAN COMPLEMENT C3); IMMUNOGLOBULIN IgG, IMMUNOGLOBULIN IgA, AND IMMUNOGLOBULIN IgM (Tables XXIII*a*, *b*)

These data also relate only to those patients with rheumatoid and non-rheumatoid eye inflammation. The mean values for rheumatoid episcleritis and rheumatoid scleritis, and non-rheumatoid episcleritis and non-rheumatoid scleritis, all fall within the normal range for each of these investigations. Tables XXIII*a*, *b* record the occasional readings which do not fall within the normal range. These variants predominated in the investigation of 1c/1a globulin, where six patients with rheumatoid episcleritis or rheumatoid scleritis and six patients with non-rheumatoid episcleritis and non-rheumatoid scleritis had depressed levels.

BACTERIOLOGY; VIROLOGY, AND MYCOLOGY

Examination of the conjunctiva for bacteria, viruses, and fungi was carried out only in those patients seen at the Tennent Institute of Ophthalmology.

One patient with non-rheumatoid episcleritis had a coagulase-negative staphylococcus. One patient with rheumatoid scleritis and one patient

Table XXII *R_3 titres*

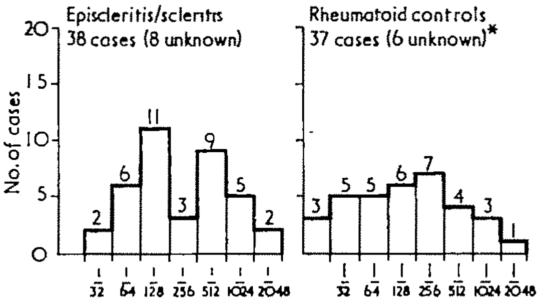


Table XXIIIa *βlc/βla globulin and immunoglobulins I$_g$G, I$_g$A, and I$_g$M in rheumatoid episcleritis and rheumatoid scleritis*

Globulin or immunoglobulin	*Rheumatoid episcleritis*							*Rheumatoid scleritis*							
					Outside normal							*Outside normal*			
	Cases (no.)	*Mean (mg/100 ml)*	*SD*	*SEM*	*Below*		*Above*	*Cases (no.)*	*Mean (mg/100 ml)*	*SD*	*SEM*	*Below*		*Above*	
					No.	*Per cent*						*No.*	*Per cent*	*No.*	*Per cent*
βlc/βla globulin	8	126·5	±44·1	±15·6	2	25·0	—	33	142·3	±36·7	±6·4	4	12·1	2	6·1
Immunoglobulin I$_g$G	7	1365·7	±546·4	±206·5	—		—	33	1717·3	±790·2	±137·6	1	3·0	2	6·1
I$_g$A	7	391·4	±152·8	±57·8	—		—	33	488·5	±259·3	±45·2	—		3	9·1
I$_g$M	7	141·7	±57·8	±21·9	—		—	33	193·3	±112·0	±19·5	—		—	

Normal values: βlc/βla globulin 100–190 mg/100 ml; immunoglobulin I$_g$G 560–2800 mg/100 ml; immunoglobulin I$_g$A 104–845 mg/100 ml; immunoglobulin I$_g$M 54–443 mg/100 ml

Table XXIIIb *βlc/βla globulin and immunoglobulins I$_g$G, I$_g$A and I$_g$M in non-rheumatoid episcleritis and non-rheumatoid scleritis*

Globulin or immunoglobulin	*Non-rheumatoid episcleritis*							*Non-rheumatoid scleritis*							
					Outside normal							*Outside normal*			
	Cases (no.)	*Mean (mg/100 ml)*	*SD*	*SEM*	*Below*		*Above*	*Cases (no.)*	*Mean (mg/100 ml)*	*SD*	*SEM*	*Below*		*Above*	
					No.	*Per cent*						*No.*	*Per cent*	*No.*	*Per cent*
βlc/βla globulin	29	134·5	±31·9	±5·9	3	10·4	—	16	148·8	±44·2	±11·0	3	18·8	1	6·3
Immunoglobulin I$_g$G	29	1225·2	±491·7	±91·3	—		—	17	1334·1	±339·4	±82·3	—		—	
I$_g$A	29	341·5	±179·7	±33·4	1	3·4	—	17	403·2	±253·6	±61·5	1	5·9	1	5·9
I$_g$M	29	169·0	±86·0	±16·0	1	3·4	—	17	202·3	±109·8	±26·7	—		1	5·9

Normal values are given with Table XXIIIa

with non-rheumatoid scleritis was a carrier of *Stayhylococcus albus.*

No case in the series had any virus cultured from the conjunctiva.

Two patients with non-rheumatoid episcleritis had fungi isolated from the conjunctiva, in both cases the *Penicillium* species. Two patients with rheumatoid scleritis had fungi present, in one case *Penicillium* and in one *Aspergillus*. One further case with non-rheumatoid scleritis produced a fungus of the *Paecilomyces* species.

MORTALITY (Tables XXIV and XXV)

The following data relate to those patients with rheumatoid episcleritis and rheumatoid scleritis, comparing them with the rheumatoid control group, matched for age, sex, and year of presentation.

Table XXIV *Mortality (rheumatoid episcleritis, rheumatoid scleritis and rheumatoid controls)* 66 *cases*

Disease	*Cases*	*Deceased*	*Percentage*
Rheumatoid episcleritis/ scleritis	33 (2 unknown)*	15	45·5
Rheumatoid controls	33 (2 unknown)*	6	18·2

Statistical analysis: $\chi^2 = 5{\cdot}6571$; $P = < 0{\cdot}025$

*These four patients could not be traced

Table XXV *Cause of death and associated disease recorded on death certificates* (17 *cases*)

	Rheumatoid episcleritis/ scleritis (11 cases; 4 unknown)		*Rheumatoid controls (6 cases)*	
	No.	*Percentage*	*No.*	*Percentage*
Myocardial infarction and congestive cardiac failure	5	45·5	4	66·7
Peptic ulceration	3	27·3	0	
Cerebrovascular accident	1	9·1	2	33·3
Bronchopneumonia	1		1	16·7
Pulmonary embolus	1		1	
Pulmonary oedema	1		0	
Hypertension	1		0	
Aortic stenosis and incompetence	1		0	
Hepatitis	1		0	
'Natural causes'	1		0	
Myeloproliferative disease	0		1	
Renal failure	0		1	
Perforated diverticulum of colon	0		1	
Diabetes (maturity onset)	0		1	

By February 1974, 15 of 33 known cases of rheumatoid episcleritis or rheumatoid scleritis

Table XXVI *Type I allergy (atopy) 23 patients*

Age (years)	*Sex*	*Diagnosis*	*Control*	*House dust*	*House dust mite (scratch test)*	*Grass pollen*	*Alternaria*	*Feathers*	*Aspergillus*	*Candida albicans*	*Cat hair*	*Dog hair*
34	Female	Episcleritis	–	–	–	–	–	–	–	–		–
40	Female	Scleritis		–	–	–	–	–	–			–
34	Female	Episcleritis		–	+	–	–	–	–	–		
37	Female	Episcleritis	–	+	++	–	–	++	–	–		
50	Female	Episcleritis	–	–	–	–	–	–	–	–		
22	Male	Episcleritis		++	++	+		+	–	–		
76	Female	Scleritis	–	–	–	–	–	–	–			
61	Female	Episcleritis	–	–	–	–	–	–	–	–		
35	Female	Episcleritis	–	–	–	–	–	–	–	–		
36	Female	Episcleritis	–	+	++	+++	–	–	–	–		
51	Female	Scleritis	–	+	+	–	–	–	–	–		
46	Male	Episcleritis		–	–	–	–	–	–	–		
47	Female	Scleritis	–	–	–	–	–	–	–	–		
67	Female	Episcleritis	–	–	–	–	–	–	–	–		
40	Male	Episcleritis		–	–	–	–	–	–	–		
40	Male	Episcleritis	–	–	–	–	–	–	–	–		
21	Male	Episcleritis	–	+	+	–	–	+	–	–	++	
34	Female	Scleritis	–	–	–	–	–	–	–	–		
49	Female	Episcleritis	–	+	++	–	–	+	–	–		–
50	Male	Episcleritis	–	–	+	–	–	–	–	–		
70	Female	Episcleritis		–	–	–	–	–	–	+		
43	Male	Scleritis	–	–	–	–	–	–	–	–		–
50	Male	Episcleritis	–	–	+	–	–	–	–	–		–

(45·5 per cent) had died since examination. The control group of patients by February 1974 gave only six of 33 known cases (18·2 per cent) who were deceased. The difference is statistically significant (P=0·025).

The details of cause of death, as recorded on the death certificates of these patients, give the expected high incidence of cardiovascular and respiratory disease. One unexpected feature was the finding that three patients of the rheumatoid episcleritis/scleritis groups (27·3 per cent) died after gastro-intestinal haemorrhage.

TYPE I ALLERGY (ATOPY) (Table XXVI)

Skin tests in 23 patients, all with non-rheumatoid eye inflammation, and all but six of them cases of episcleritis, did not suggest that there is an increased incidence of atopic disease in these patients. Of the 23 patients, four had a mild positive reaction to house dust or house dust mite, and five had positive skin tests to more than one antigen. Three of the patients with positive skin tests gave a clear history of either hay fever or asthma; the remaining patients with positive skin tests had no clinical history of type I allergy.

Discussion

OPHTHALMOLOGY

There have been few reports reviewing episcleritis and scleritis; most papers have been on individual cases of interest. Studies by Watson and Lobascher (1965), Sevel (1965), Watson (1966), Sevel (1967), Lyne and Pitkeathly (1968), Fowler (1970), Jayson and Jones (1971), with follow-up studies by Jones and Jayson (1973), Watson (1974), and Lyne (1974), are the sum total of reviews. The incidence of scleritis in rheumatoid arthritis in the study presented has some similarity with the majority of reports previously documented (Table XXVII). Jayson and Jones (1971) in a group of 142 patients had a notably dissimilar figure and Sevel's estimate of one case of scleritis in 3000 patients with rheumatoid arthritis is much lower than our own conclusions. As with the review of Jayson and Jones (1971) this present series was a prospective study for incidence. The incidence of episcleritis in patients presenting with rheumatoid arthritis has not been documented elsewhere, which is understandable as the condition is relatively uncommon, at least in so far as presentation is concerned. Only seven patients, an average of approximately one for each year of the study, are included in this group.

Table XXVII *Scleritis in rheumatoid arthritis*

Authors	*Date*	*Patients with*		*Percentage*
		Rheumatoid arthritis	*Scleritis*	
Smith	1957	465	2	0·4
Bywaters	1964	1000	1–2	0·15
Hart	1964	900	±7	0·8
Richardson	1964	1000	±3	0·3
Sevel	1965 (Estimate)	3000	1	0·03
Jayson and Jones	1971	142	9	6·3
Present study	1976	4210	28	0·67

Reports giving the incidence of rheumatoid arthritis in episcleritis and scleritis (Table XXVIII) are consistent with the findings of this study. It will be interesting to follow up the patients without apparent rheumatoid disease some years hence, particularly in view of the finding of one patient with episcleritis and six with scleritis, each of whom had a weakly positive rheumatoid factor.

A very interesting question posed by Sevel (1966) is whether scleritis has been seen more often in recent years. A histogram of his 43 cases which had presented at the Pathology Department, Institute of Ophthalmology, London, between 1950 and 1964 suggests an increased incidence of scleritis since 1954. Studies in rheumatoid arthritis suggest that the incidence of rheumatoid vasculitis has increased since the advent of treatment with systemic corticosteroids (Ferguson and Slocumb, 1961; Smyth and Gum, 1961), although this view does not have unquestioned acceptance (Schmid, Cooper, Ziff, and McEwen, 1961). It may be that the same vasculitis that is possibly related to systemic corticosteroid treatment, in particular to variations in dosage (Slocumb, 1953), has been instrumental in initiating a greater frequency of scleritis. Systemic corticosteroids were first used in the treatment of rheumatoid arthritis in 1949 (Hench, Kendall, Slocumb, and Polly, 1949) and in the treatment of scleritis in 1951 (Talkov, Colpoys, Davis, Papper, and Fienberg, 1951).

The only reports giving the mean age of patients with scleritis in rheumatoid arthritis are those of Sevel (1966), and Jayson and Jones (1971). The nine patients of Jayson and Jones had a mean age of 56·5 years, which is similar to the figure given here (Table III*a*). Sevel's series of 11 cases with rheumatoid scleritis had a mean age of 64·1 years, but these were eyes which required enucleation, and so were particularly severe examples. Nine patients in our study with rheumatoid episcleritis gave an almost exactly similar mean age as the patients with rheumatoid scleritis (Table III*a*). Non-rheumatoid inflammation presented a lower mean age, particularly for episcleritis (Table III*b*). Lyne and Pitkeathly (1968) reported a similar picture in 55 cases of episcleritis with men having a mean age of 45 years and women 48 years, but their figures included three cases of rheumatoid arthritis. Their 31 cases of scleritis, including nine cases of rheumatoid arthritis, had a mean age of 49 years for men and 50 years for women. It may be that rheumatoid episcleritis and scleritis tend to affect a slightly older age-group of patients with rheumatoid disease. Two of us (JW and DDMM) examined a group of 148 patients with rheumatoid arthritis for evidence of steroid-induced cataract, and their mean age was 52·5 years. The control group of 159 patients with rheumatoid arthritis, who had never been treated with systemic corticosteroids, had a mean age of 49·3 years (Williamson, Paterson, McGavin, Jasani, Boyle, and Doig, 1969). In the progression of the disease the most severe cases affect an even older age-group; this was evident in the pathological series of Sevel (1966). The predominance of women with rheumatoid ocular inflammation (Table III*c*) reflects the higher incidence of women with rheumatoid arthritis, a ratio of 2 or 3:1 (Boyle and Buchanan, 1971), and this agrees with previous studies (Sevel, 1965; Jayson and Jones, 1971). Non-rheumatoid inflammation presents us with an intriguing problem. The report of Lyne and Pitkeathly (1968), with only three cases of rheumatoid arthritis in their 55 cases of episcleritis, supports the evidence of this study that non-rheumatoid episcleritis occurs equally in the sexes (Table III*d*). If episcleritis is due to immune-complex disease and has a similar basis in this respect to scleritis, as suggested by Jones (1971), why is there such a notable difference in the respective sex ratios? The sex ratio in non-rheumatoid scleritis (Table III*d*), together with the finding that one-third of these patients had a weakly positive rheumatoid factor (one was a man), gives some concern for the future of these patients.

Table XXVIIIa *Rheumatoid arthritis in scleritis*

Authors	*Date*	*Patients with*		*Percentage*
		Scleritis	*Rheumatoid arthritis*	
Watson	1966	108	35	32·4
Lyne and Pitkeathly	1968	31	9	29·0
Present study	1976	27	9	33·3

Table XXVIIIb *Rheumatoid arthritis in episcleritis*

Authors	*Date*	*Patients with*		*Percentage*
		Episcleritis	*Rheumatoid arthritis*	
Watson	1966	117	4	3·4
Lyne and Pitkeathly	1968	55	3	5·5
Present study	1976	35	2	5·7

An unusual connective-tissue disorder seen in the present study, in a 45-year-old man with rheumatoid scleritis, presented with widespread granulomas of orbits, nasal septum, sinuses, and lungs, which had occurred intermittently for more than 10 years. The clinical picture was less severe than that of a true Wegener's disease, and lacked the glomerulonephritis typically present in this disease (Godman and Churg, 1954). A chronic dacryocystitis eventually required dacryocystectomy; histological examination showed no necrotizing vasculitis but did show that finger-tip vasculitis, subcutaneous nodules, and skin ulceration had occurred. This case may fall into the category of a limited form of Wegener's disease, as described by Carrington and Liebow (1966) in 16 patients, nine of whom had pulmonary lesions only. Four similar cases have been reported more recently (Cassan, Coles, and Harrison, 1970). Other connective-tissue disorders found in the non-rheumatoid groups of patients were chronic discoid lupus erythematosus associated with episcleritis, and systemic lupus erythematosus associated with scleritis (one case of each). There is some doubt whether these two conditions are separate entities, although systemic manifestations are rare in the chronic discoid form of lupus erythematosus (Boyle and Buchanan, 1971). Systemic lupus erythematosus has been described previously in two cases of episcleritis by Harvey, Shulman, Tumulty, Conley, and Schoenrich (1954) and in isolated reports by Larson (1961) and Spaeth (1967). Associated scleritis has been reported in two cases (Sevel, 1965; Watson, 1966). No previous paper gives episcleritis as a complication of chronic discoid lupus erythematosus.

In the late nineteenth and early twentieth century, gout was considered to be an important cause of ocular inflammation, but the association in most cases of episcleritis or scleritis is vague and indefinite (Duke-Elder and Leigh, 1965). During this century reports of episcleritis have been recorded by Gilbert (1914), Savin (1938), and McWilliams (1952). In recent years only Watson and Lobascher (1965) reported one case with an episcleritis. Two male patients with gout were seen in the present study; one with non-rheumatoid episcleritis and one with a non-rheumatoid necrotizing scleritis. The necrotizing element developed some weeks after the onset of scleritis, and might have been iatrogenic in origin. The patient had a diffuse scleritis which progressed to develop widespread scleral translucency in the upper half of the anterior sclera. A subconjunctival injection in the upper and lower fornices was followed by an area of necrosis above (Fig. 3). The eye subsequently settled satisfactorily. Subconjunctival injections of atropine have been incriminated in the aetiology of scleritis (Tooker, 1931; Swan and Butler, 1951). Three of the five cases of Swan and Butler had skin sensitivity reactions to atropine.

Erythema nodosum, a condition previously associated with episcleritis (McCarthy, 1961) and reported with scleritis (Watson and Lobascher, 1965) was evident in two women with non-rheumatoid episcleritis, and one woman with non-rheumatoid scleritis. There are many common disorders associated with erythema nodosum, including streptococcal infection, sarcoidosis, tuberculosis, drug reactions (for example, to sulphonamides), rheumatic fever, gonorrhoea, lymphogranuloma inguinale, and coccidioidomycosis (Fry, 1952). James (1961) could not give any aetiological factor in only 23 of 170 cases of erythema nodosum. He found evidence of sarcoidosis in 126 and infection, usually streptococcal, in 21. None of the three patients in this study had a raised ASO titre or any definite history of the conditions listed. The episcleritis in both cases was 'simple', but the patient with scleritis had a nodular lesion. An anterior uveitis was present in the case of nodular scleritis, and this has been documented previously (Allan, 1901). Duke-Elder and Leigh stated that scleral keratitis was a rarity, citing Palich-Szanto (1959). One of the cases of episcleritis, which was bilateral, had associated bilateral sclerosing keratitis.

It is uncertain why many patients with rheumatoid episcleritis and rheumatoid scleritis had a marked increase in electrocardiographic abnormalities (Table IV*a*). It is possible that the changes, which include bundle-branch block myocardial infarction, and non-specific S-T wave changes, might have been in part, at least, due to rheumatoid involvement of the heart, but without necropsy it is impossible to differentiate between rheumatoid disease, induced ischaemia, and other causes of ischaemic heart disease (Hart, 1969). Pitkeathly, Howitt, and Lyne (1970) documented three cases of aortic incompetence in patients with scleritis, one of whom had a history of polyarthritis of uncertain origin. They presented the scleritis and aortic incompetence as two manifestations of connective-tissue disease. Both patients had right bundle-branch block; this conduction defect was found in three patients with rheumatoid scleritis. A further case of aortic incompetence associated with rheumatoid scleritis was described by Jones and Jayson (1973) in their follow-up study (Jayson and Jones, 1971). In one male patient in this study with diffuse rheumatoid scleritis aortic stenosis and incompetence were discovered *post mortem.* One with rheumatoid episcleritis had aortic stenosis and one with non-rheumatoid scleritis had aortic incompetence. None of these patients had a history of rheumatic fever. According to Sokoloff (1972) rheumatoid disease may occasionally cause a valvulitis with incompetence (Van Valkenburgh, Georges, and Irby, 1972). Pericarditis has been described in association with rheumatoid arthritis and scleritis (Smoleroff, 1943; Edstrom and Osterlind, 1948; Jayson and Jones, 1971). Two patients in the present study had clinical evidence of pericarditis; one had rheumatoid scleritis and the other non-rheumatoid episcleritis. Pericarditis is a recognized complication of rheumatoid disease (Harrold, 1968; Bacon and Gibson, 1974) and it was noted by Bonfiglio and Atwater (1969) that patients with pericarditis more often had severe joint disease. Kirk and Cosh (1969) found that 10 of 100 patients with rheumatoid arthritis had clinical features of pericarditis.

A striking increase in pulmonary complications – such as pleurisy, pneumonitis, pleural effusion, and rheumatoid nodules – was apparent in patients with rheumatoid episcleritis and rheumatoid scleritis (Table IV*a*). Pleural effusion is a recognized entity in rheumatoid disease (Carr and Mayne, 1962; Walker and Wright, 1967). This complication occurs in severe rheumatoid disease as manifested by the presence of subcutaneous nodules (Boyle and Buchanan, 1971). Pulmonary nodules are themselves not uncommon (Noonan, Taylor, and Engleman, 1963). This significant finding of pulmonary disease in patients with rheumatoid eye inflammation as compared with rheumatoid controls, together with the possibility of greater cardiac involvement, emphasizes the serious nature of extra-articular rheumatoid disease affecting vital structures with the probable final seal of significance in the higher incidence of mortality in patients so affected.

There is an increasing appreciation of the association of ocular inflammation and joint disorders in patients with inflammatory bowel disease. Wright, Lumsden, Luntz, Sevel, and Truelove (1965) found that 11·8 per cent of 144 patients with ulcerative colitis had iritis, and 17·4 per cent had sacro-iliac joint abnormalities. Billson, de Dombal, Watkinson, and Goligher (1967) substantiated the association of eye inflammation and ulcerative colitis, and Jayson, Salmon, and Harrison (1970) found that 50 per cent of patients with ankylosing spondylitis and colitis had an anterior uveitis. Lyne and Pitkeathly (1968) reported two patients with ulcerative colitis associated with scleritis, but without any connective-tissue disorder. Watson (1966) described one case of regional ileitis associated with episcleritis, and Hopkins, Horan, Burton, Clamp, de Dombal, and Goligher (1974) recorded two patients with episcleritis associated with regional ileitis. One patient in the present study with rheumatoid episcleritis had recurrent colitis, and one with rheumatoid scleritis had diverticulosis; both were women. The patient with recurrent colitis had an associated anterior uveitis; the patient with diverticulosis had a particularly severe bilateral scleritis with sclerosing keratitis, anterior uveitis, and secondary glaucoma in one eye. However, while it is reported that patients with ulcerative colitis and uveitis have a threefold increase in peripheral joint disease (Wright and Watkinson, 1965; McEwen, 1968) the arthritis is regarded in most instances as distinct from rheumatoid arthritis. It has been called arthritic ulcerative colitis (Ruhl and Sokoloff, 1965) and colitic arthritis or acute toxic arthritis (Fernandez-Herlihy, 1959). Regional ileitis (Crohn's disease) exhibits the same type of peripheral arthritis (Ferguson, 1972). This form of arthritis was first described by Hench (1935). It begins abruptly and reaches its height of intensity within the first day or so, involving the small joints of hands or feet less often than does rheumatoid arthritis (Wright and Watkinson, 1965).

It has been suggested that peptic ulceration occurs more commonly in rheumatoid arthritis (Atwater, Mongan, Wieche, and Jacox, 1965; Bowen, Mayne, Caine, and Bartholomew, 1960; Meltzer, Bockman, Kanenson, and Cohen, 1958), but both are such common diseases that it is unwise to be dogmatic. Four of our patients with rheumatoid scleritis had peptic ulceration and three of the 11 known to have died since examination had gastrointestinal haemorrhage recorded on their death certificates. If the association is valid, is it caused by a vasculitis or is it a therapeutic consequence of, for example, salicylates? Certainly all three patients who died of gastrointestinal haemorrhage had been receiving salicylates. Against this it is noteworthy that four patients with non-rheumatoid episcleritis, that is without severe disease, also had a history of peptic ulceration.

Skin diseases reported with episcleritis are eczema (Watson and Lobascher, 1965), contact dermatitis and acne rosacea (Watson, 1966), psoriasis, lichen planus, and erythema elevatum diutinum (Lyne and Pitkeathly, 1968); and with scleritis, epidermolysis bullosa dystrophica (Mazza and Panagis, 1967). Erythema nodosum, which has already been discussed, has been associated with both episcleritis and scleritis. Psoriasis was evident in two women in the study, one with rheumatoid scleritis and one with non-rheumatoid episcleritis. There were no secondary eye complications in either of the patients with psoriasis. A further patient with non-rheumatoid episcleritis had a history of pityriasis rosea.

Reviewing the literature of scleritis in rheumatoid arthritis, Sevel (1966) found that the condition was more often bilateral. The ratio of 2:1 agrees with the findings given here (Table III*e*). In his own series of 11 enucleated eyes, the disease was unilateral in eight, an inconsistency which Sevel was unable to explain. Extra-articular manifestations of rheumatoid disease are significantly apparent in this present study and the fact that in most cases rheumatoid scleritis is bilateral reflects the widespread nature of extra-articular involvement. Non-rheumatoid scleritis was more often unilateral and whether or not these patients will later develop autoimmune disease, it seems that they have a more localized disorder. Non-rheumatoid episcleritis in contrast was more often bilateral

(Table III*f*) and characteristically recurrent, with inflammation alternating from one eye to the other.

It is generally recognized that the symptoms of episcleritis are less distressing than those of scleritis (Watson and Lobascher, 1965; Jayson and Jones, 1971). One of the objects of this presentation was to provide evidence that these accepted differences do exist. Ocular pain was more apparent in scleritis. The patients complained of a red eye more often in both rheumatoid and non-rheumatoid episcleritis than did those with scleritis (Tables V*a*, *b*). A distinctive finding was the higher incidence of complaints of redness and pain in non-rheumatoid inflammation. Perhaps the rheumatoid patient suffers to such a degree elsewhere that the spontaneous complaint of a red and painful eye is not always given. However, Jones and Jayson (1973) pointed out that the fewer complaints in patients with rheumatoid eye inflammation might be due to the many anti-inflammatory drugs which these patients were receiving, or possibly the higher pain threshold which has been described in rheumatoid arthritis (Huskisson and Hart, 1972). In his early description of 'sclerotitis', Mackenzie (1830) reported that a number of patients described their eyes as hot and dry at the onset of an episode of inflammation. It was interesting to discover a few patients in this study who said that a dry, gritty, or burning eye would often precede the flare-up of inflammation.

It was surprising to find that the history of eye inflammation was slightly longer in the non-rheumatoid group of patients, both for episcleritis and scleritis (Table VI*b*). A simple explanation might be the problem of recollection. Many patients were examined early in the disease, but not all. With so many physical disabilities in what is generally severe rheumatoid disease, the rheumatoid patient might simply have misjudged how long the eye trouble had lasted. Lyne and Pitkeathly (1968) gave a mean duration for all forms of episcleritis of 20 months and a mean duration for all forms of scleritis of 60 months. The difficulty is knowing when an eye is truly quiet and will remain so. Many patients in this study had quiescent periods between inflammation lasting many months, and in one case seven years. Nevertheless, a rather uneasy impression given by the rheumatoid patients is of the disease 'burning out' after two or three years.

As expected, the deeper inflammation of scleritis has a more significant effect on visual acuity (Table VII). The study of visual acuity was confined to patients presenting at the Tennent Institute of Ophthalmology as cases of episcleritis or scleritis, and did not include patients presenting with rheumatoid arthritis at the Centre for Rheumatic Diseases. Visual acuity in these patients was affected mainly by anterior segment disease, particularly corneal inflammation and cataract. The review of posterior subcapsular cataract/advanced cataract in rheumatoid patients with scleritis who were receiving systemic corticosteroids also suggests, although without supporting figures, a severe effect on visual acuity (Table XII). Furthermore, the group of patients with rheumatoid scleritis who had a posterior segment abnormality would have some disturbance of vision (Table XIII*a*). Fortunately, a cataract can readily be extracted and this should provide some reassurance to the clinician who considers that treatment with systemic corticosteroids is imperative. The male patient who developed gout, and subsequently scleritis, recorded a visual acuity which dropped from 6/6–2 to 6/18–1 in four weeks, due to the development of a variable myopic astigmatism. This eventually settled coincident with quiescence of his scleritis as a mixed astigmatism which, on refraction, gave a visual acuity of 6/5, a reminder that reduction in vision might have had a very simple solution.

The abundance of terms used to describe episcleritis and scleritis requires a new simplicity of approach, and this was provided by the classification of Watson, Hayreh, and Awdry (1968a, b), which was used in this study (Tables VIII*a*, *b*). Clearly the pathological activity in scleritis and nodular episcleritis has the same basis (Manschot, 1961; Sevel, 1967), and it only remains to give a description of the appearance of any inflammation. There has been much confusion regarding the terms 'scleromalacia' and 'scleromalacia perforans' (Van der Hoeve, 1934). 'Scleromalacia' is often used for a diffuse scleritis with scleral translucency, but this is not the eye which is the most likely to perforate, and so confusion results. According to the literature the eye which commonly perforates has a typically necrotizing sclera, and the inflammation is necrotic and the sclera opaque but not translucent (Fig. 3). Most reports of scleromalacia perforans give a distinct destructive picture to the scleral lesion, describing such features as necrosis, sloughing, or ulceration (Van der Hoeve, 1934; Oast, 1937; Verhoeff and King, 1938; Harbater, 1949; Shanedling, 1950; François, 1951; Talkov and others, 1951; Ashton and Hobbs, 1952; Renard, Lelièvre, and Mazel, 1953; Ellis and Holtz, 1953; Armstrong and McGovern, 1955; Marquard, 1956; Boberg-Ans, 1958; Williams and Rosenthal, 1959; Taffet and Carter, 1961; François, Victoria-Troncoso, Hanssens, and Bakskulin, 1969; Gombos, 1967). Blum and Salmoun (1963) and Merz (1964) reported cases where scleral translucency with alarming progressive ectasia necessitated surgical intervention. In these cases there was no necrosis or ulceration.

The importance of these observations is the appreciation that areas of scleral translucency only rarely give cause for concern. Rheumatoid nodule of the sclera was the term used by Ashton and Hobbs (1952) to describe the scleritis found in rheumatoid arthritis. It gives an accurate description of the granulomatous reaction, similar to that found in the subcutaneous nodule of rheumatoid arthritis. However, a sub-division of the lesions into nodular, diffuse, or necrotizing scleritis provides a clear and simple picture of the scleral reaction with the premise that the inflammation is granulomatous. The overall descriptive term for scleritis which satisfies the pathological uniformity of the condition is necrogranulomatous scleritis (Sevel, 1967). It is interesting that none of our cases of rheumatoid episcleritis was nodular in character, whereas in non-rheumatoid episcleritis nearly one-fifth of cases were nodular (Tables VIII*a*, *b*). Two cases of rheumatoid inflammation initially diagnosed as nodular episcleritis both progressed to a scleritis. Only one patient in the study presented with a necrotizing scleritis. A 63-year-old man developed a non-rheumatoid gouty scleritis, but the necrotizing lesion discussed earlier was probably induced by a subconjunctival steroid injection. Duke-Elder and Leigh (1965) described the possibility of recurrent nodular episcleritis causing the circumcorneal region of the sclera eventually to become slate-coloured. We submit that any appearance of this nature is due to involvement of the sclera and is no longer an episcleritis but a scleritis. The two patients diagnosed initially as having nodular rheumatoid episcleritis subsequently had a distinct slate-coloured zone at the site of inflammation, and were therefore cases of scleritis.

Transparency of the sclera which may accompany scleritis is often described as scleral thinning. This description may create apprehension in the mind of the clinician, and a term such as scleral translucency is preferable. In a recent presentation involving one of us (DDMM), ultrasonographic assessment of the thickness of areas of post-scleritic scleral translucency showed that these areas were not invariably associated with thinning. Only three of eight patients had distinct evidence of thinning of sclera (Rooney, McGavin, Sutherland, and Railton, 1974). The presence of translucency of the sclera reflects the depth and extent of the scleral inflammation, which in this study was very much more evident in rheumatoid scleritis, indicating that scleritis in rheumatoid disease is generally more severe (Tables VIII*a*, *b*). Posterior scleritis is more common in patients with rheumatoid arthritis which also suggests a more extensive inflammation in rheumatoid disease. Inflammation of the posterior sclera is deduced from its secondary effects on neighbouring tissues. Posterior inflammation resulted in choroiditis in two patients, retinal detachment in one, and extraocular muscle imbalance in five. In a paper on the clinical manifestations of scleritis, Watson (1974) found that of 217 eyes with episcleritis, 170 had the simple variety and 47 had nodular episcleritis. Of 301 eyes with scleritis, 119 had diffuse anterior scleritis, 134 had nodular anterior scleritis, 42 showed necrotizing scleritis, and six revealed features of a posterior scleritis. This series, easily the largest general study of episcleritis and scleritis, is particularly significant for its record of the clinical features of these conditions.

Lyne and Pitkeathly (1968) noted that single attacks of episcleritis affected the interpalpebral area in 25 of 33 cases. This distribution of inflammation is substantiated by the present study (Tables IX*a*, *b*). Lyne and Pitkeathly suggested that minor trauma might account for this distribution and found a foreign body in one case. Certainly external factors would seem to play a part, whether trauma or some other factor or factors. Patients sometimes complain of a dry, gritty, and burning eye and epiphora was seldom a problem. An eye which is inflamed primarily deep to the conjunctiva may slightly increase in temperature. Evaporation of tears may ensue more rapidly in consequence and so irritation due to exposure will affect the interpalpebral area preferentially. However, this could account only for aggravation of an already inflamed area. It was thought that type I allergy (atopy) might play a part in the external aggravation of an episcleritis. However, in the present study no increase in atopic disease could be found in 23 patients with non-rheumatoid eye inflammation, 17 of whom had episcleritis. Inflammation affecting the anterior sclera in rheumatoid arthritis affects the upper half of the sclera more often than the lower half (Jayson and Jones, 1971), and Sevel's review of the literature confirms this view. Sevel (1965) in his 11 cases examined histologically, found that 18·0 per cent had disease of the posterior segment, and his investigation of the literature with regard to eyes enucleated because of scleritis gave a figure of 12·0 per cent. These figures are not dissimilar to our own for rheumatoid scleritis (Table VIII*a*). However, the distribution of anterior scleritis in this report, although more often affecting the superior aspect of the sclera, does not have the considerable emphasis of Sevel's cases (Table IX*a*). Jayson and Jones (1971) in their group of 14 patients found a distribution similar to that seen in our study.

Corneal complications in scleral inflammation have been described for over a century (Mackenzie, 1830). The predominant disturbance is a sclerosing keratitis which, according to Watson, Hayreh, and Awdry (1968a), occurs in nearly half of those patients with scleritis but seldom in those with episcleritis. In 11 cases which were enucleated and comprised the series of rheumatoid scleritis (Sevel, 1965), 36·0 per cent had some form of keratitis. However, rheumatoid episcleritis and rheumatoid scleritis in this investigation showed a high incidence of corneal complications (Table X*a*), in particular sclerosing keratitis (Fig. 4), and it was interesting to find that anterior uveitis although less common had a similar incidence in rheumatoid episcleritis and rheumatoid scleritis, unexpected findings as regards episcleritis. The anticipated difference between episcleritis and scleritis was confirmed in regard to cataract, glaucoma, and posterior segment disease, but it will be recalled that only 13 eyes had rheumatoid episcleritis. Corneal ulceration occurred in two forms; limbal guttering (Fig. 5), which has been called marginal furrows (Brown and Grayson, 1968), and keratolysis. While limbal guttering may persist for a considerable time, and during the active phase of scleral inflammation appears to 'creep' around the limbus, keratolysis is a more dramatic 'melting' of the cornea which may result in loss of the anterior chamber with iris prolapse. Watson and Holt-Wilson (1974) described a further corneal complication of scleritis which they called deep keratitis, in which a deep sheet opacity with deep vascularization after long-standing recurrent scleritis was evident. We have recently seen a young woman with non-rheumatoid scleritis, who is not included in this study, where this striking corneal complication was present.

The main feature of interest in the patients with anterior uveitis was the higher incidence of posterior synechiae in patients with rheumatoid scleritis as compared with non-rheumatoid scleritis. This would suggest a more active and tenacious form of uveal inflammation, which is consistent with the impression of severe ocular disease in rheumatoid arthritis. However, the presence of anterior uveitis in both rheumatoid and non-rheumatoid inflammation was very nearly as common in episcleritis as in scleritis. Anterior uveitis occurred in approximately one-fifth of patients with episcleritis and it occurred in about one-quarter of those with scleritis (Tables XI*a*, *b*). Iridocyclitis has often been described with scleritis (Wolfe, 1882; Kiehle, 1946; Duke-Elder and Leigh, 1965). Sevel (1965) in his series of 11 rheumatoid cases found histological evidence of cyclitis in 46·0 per cent. The figures given in this study are objective in that they indicate evidence of active or old uveitis (for example, posterior synechiae), and so the true figure will be higher. A deep scleritis will invariably be accompanied by uveitis—whether iritis, cyclitis, or choroiditis—but a number of cases, particularly in the anterior segment, may settle without any residual evidence of inflammation.

Posterior subcapsular cataracts have been reported in 10·5 to 60 per cent of patients with rheumatoid arthritis receiving treatment with long-term oral corticosteroid therapy (Black, Oglesby, von Sallmann, and Bunim, 1960; Giles, Mason, Duff, and McLean, 1962; Crews, 1963; Irby, Toone, Wittkamp, and Wiesinger, 1964; Spencer and Andelman, 1965; Furst, Smiley, and Ansell, 1966). A similar study at the Centre for Rheumatic Diseases, Glasgow, provided an incidence of steroid-induced cataract of 11·5 per cent (Williamson and others, 1969). The combination of treatment with systemic corticosteroids and the presence of anterior segment inflammation in the form of scleritis carries a high risk of the development of cataract; in this study, an incidence of 36·0 per cent (Table XII). While it is helpful to be aware of this possible complication, it is reassuring that where systemic corticosteroid treatment is clearly indicated, any resulting cataract can be removed by surgery.

Posterior scleritis can provoke various intraocular side-effects including choroiditis with exudative retinal detachment (Radnót, 1948; Harper, 1960; Hurd, Snyder, and Ziff, 1970), macular oedema (Watson and Lobascher, 1965), retinal striations (Sears, 1964) and optic disc oedema (Bertelsen, 1960). Orbital myositis is an extraocular manifestation (Gorduren, 1962; Maria, 1956). In his pathological series, Sevel (1965) found choroiditis (64·0 per cent), choroidoretinitis (9·0 per cent) and retinal detachment (64·0 per cent). Rheumatoid scleritis provides disturbing indications of deep-seated inflammation, posterior segment abnormality affecting nearly one-third of the patients (Table XIII*a*). Although macular disturbance could have other causes, such as drug-induced maculopathy, senile degeneration (Bedell, 1950; Favre, 1960) and vascular disease (Norn, 1961) it is recognized that it may occur with retinitis (Manschot and Von Winning, 1953) or iridocyclitis (Samuels, 1930; Wolff, 1931). It is possible, therefore, that the large number of rheumatoid patients with a macular disturbance may be attributed, in part at least, to the consequence of severe scleritis, the incidence being higher than in the non-rheumatoid patients with scleritis, both groups having a mean age in the sixth decade. The uveitis accompanying a scleritis is more often an anterior uveitis, but whether anterior or posterior it is from this serious complication that most of the consequent ocular problems arise, problems which affect vision – such as cataract, glaucoma, exudative retinal detachment, and macular disturbance. Optic nerve disease after scleritis has had little documentation. Bertelsen (1960) described 12 patients with a posterior scleritis and two of these had oedema of the optic nerve head. The cases of Gorduren (1962) and Maria (1956) of sclerotenonitis and orbital myositis both had optic nerve oedema with associated retinal oedema. One patient in the present series with a rheumatoid scleritis had optic disc oedema.

Watson (1966) found that seven of 108 cases with scleritis (6·5 per cent) had raised intraocular pressure, and Sevel (1965) in his study of enucleated eyes reported that 45·0 per cent of 43 cases had a history of secondary glaucoma. Watson's cases settled with the good response of the scleritis to systemic treatment. He stated that surgery was avoided because of the dangers of aggravating the inflammation. Apart from one case of non-rheumatoid episcleritis with an intraocular pressure fractionally above the upper limit of the normal range, all cases of secondary glaucoma in this study were in patients with scleritis (Tables XIV*a*, *b*). As in Watson's series (1966), the intraocular pressure settled coincident with quietening of the scleritis in most cases. One patient required surgery and one patient, with a minimally raised pressure (22 mmHg), is still receiving medical treatment. If the indications for operative intervention become compelling, surgery should be carried out despite the presence of inflammation. The patient with rheumatoid arthritis and severe scleritis who required surgery underwent a drainage procedure without any exacerbation of inflammation.

The deeper and more extensive inflammation of scleritis affects ocular movement considerably more often than episcleritis, and one suspects that the latter may affect movement only because of the discomfort sustained in moving the eye to the affected side (Tables XV*a*, *b*). There is a close association of scleritis, in particular posterior scleritis, with tenonitis, myositis, and pseudotumour formation. (Although orbital myositis has been called a form of pseudotumour the differentiation in terms seems more appropriate.) It is sometimes difficult to reach the correct diagnosis in these conditions. The patient presents with pain, limitation of ocular movement, chemosis, and sometimes lid oedema. The indirect consequence of inflammation provides the clue to diagnosis, and this appearance will often simulate orbital cellulitis. Bertelsen (1960) confesses to this mistake in six of his 12 patients with sclerotenonitis and orbital myositis. Both Gorduren (1962) and Maria (1956) began treatment with systemic antibiotics in their cases before reaching the true diagnosis. Coop (1961) in a series of 47 cases of orbital pseudotumour found nine which presented with chemosis as part of the clinical picture. In the woman with non-rheumatoid scleritis who presented with strabismus there was the same confusion in diagnosis. A biopsy of the central strip of tendon/muscle of the lateral rectus muscle confirmed the diagnosis. There was no untoward effect on the inflammation as a result of surgical intervention.

The incidence of Sjögren's syndrome in rheumatoid arthritis has been estimated at between 9 and 34 per cent, and in the sicca syndrome there is a 60 to 75 per cent incidence of connective-tissue disease (Henkind and Gold, 1973). Talal (1972) considers that keratoconjunctivitis sicca develops in 10 to 15 per cent of patients with rheumatoid arthritis and cites the report of Stenstam (1947). While the incidence of keratoconjunctivitis sicca in the present study in patients with rheumatoid episcleritis and rheumatoid scleritis falls within the accepted range for rheumatoid arthritis, the incidence of Sjögren's syndrome is considerably higher than that found by Williamson (1970) in patients with rheumatoid arthritis, also attending the Centre for Rheumatic Diseases. He found that between 6 and 7 per cent of patients with rheumatoid arthritis had Sjögren's syndrome. The incidence given here in rheumatoid episcleritis (33·3 per cent) and rheumatoid scleritis (32·4 per cent) reflects the extent of extra-articular manifestations in patients with rheumatoid episcleral and scleral inflammation.

RHEUMATOLOGY

It is not the purpose of this paper to discuss the rheumatological findings in any detail. However, some of the results of this aspect of our study lead us to suspect that the underlying disease of scleritis in these patients may be a vasculitis.

The arthritis in patients with rheumatoid episcleritis and rheumatoid scleritis was of longer duration and revealed more severe erosive changes on *x*-ray examination as compared with the rheumatoid controls (Table XVII). On the other hand, the functional capacity and the degree of joint tenderness were similar in the rheumatoid patients with and without inflammatory eye disease. Subcutaneous nodules in rheumatoid arthritis are found in approximately one-third of patients (Boyle and Buchanan, 1971). Of the patients with rheumatoid episcleritis and rheumatoid scleritis 50 per cent had subcutaneous nodules, twice the percentage found in the control group of patients (Table XVIII). Histological studies of early nodule formation by Sikoloff, McCluskey, and Bunim (1953) suggest that the nodule develops around an inflamed blood vessel. It is significant that biopsy of episcleral nodules in patients with rheumatoid arthritis has given a pathological picture similar to that of the subcutaneous nodule of rheumatoid arthritis (Edstrom and Osterlind, 1948; Mundy, Howard, Stillman, and Bevans, 1951; Ferry, 1969), and examination of enucleated eyes with scleritis has confirmed a uniform basic pathology (Manschot, 1961; Sevel, 1965).

Approximately 25 per cent of patients with rheumatoid arthritis have vasculitis on *post-mortem* examination (Cruickshank, 1954). Rheumatoid vasculitis, unlike classical polyarteritis nodosa, spares the kidneys, and hypertension and asthma are rare (Ferguson and Slocumb, 1961). It is interesting that while respiratory disease and possibly cardiac involvement were features notable in the patients with rheumatoid eye inflammation, renal disease was not a problem. Rheumatoid vasculitis affects the peripheral nerves (Hart, Golding, and McKenzie, 1957; Ferguson and Slocumb, 1961; Wilkinson and Torrance, 1967), giving rise to a sensory and/or motor neuropathy (Hart and Golding, 1960; Schmid and others, 1961) and to dermal infarction (Bywaters, 1957; Golding, Hamilton, and Gill, 1965). In the group of patients with rheumatoid episcleritis and rheumatoid scleritis, 8·9 per cent had a peripheral neuropathy, presumably due to vasculitis affecting the vasa nervorum, and 13·3 per cent had skin ulcers, both incidences very much higher than expected, although for these numbers there was no statistically significant increase in the incidence of peripheral neuropathy or skin ulcers as compared with that in rheumatoid controls (Table XVIII).

Many patients with rheumatoid scleritis also manifested skin bruising and skin atrophy (Table XVIII), features almost certainly attributable to systemic corticosteroid treatment, which most of the patients were receiving (Boyle and Buchanan, 1971). It has been suggested that systemic corticosteroids produce alteration in the dermal connective tissue, particularly in collagen (Scarborough and Schuster, 1960; Greenwood, 1966).

Patients with rheumatoid ocular inflammation also had a high incidence of splenomegaly (10·9 per cent) (Table XVIII). All five patients with splenomegaly had anaemia and two of the patients had a neutropenia. The syndrome of chronic rheumatoid arthritis, splenomegaly, and neutropenia, first described by Felty (1924), is said to occur in fewer than 5 per cent of patients with rheumatoid arthritis (Walker and Wright, 1968).

The picture that emerges in the patient with rheumatoid episcleritis and rheumatoid scleritis is that of long-standing rheumatoid disease and severe erosive joint changes on *x*-ray examination, with many extra-articular manifestations of rheumatoid disease, many of which reflect an underlying rheumatoid vasculitis. Episcleritis and scleritis in these patients is further evidence of widespread and severe disease affecting eyes, peripheral nerves, skin, lungs, and possibly the heart. These findings substantiate the reports of Jones and Jayson (1973), who found a significant incidence of rheumatoid subcutaneous nodules and other features of microvasculitis in patients with rheumatoid scleritis.

LABORATORY INVESTIGATIONS

Laboratory data confirm the expected evidence of widespread disorder in patients with rheumatoid disease as compared with patients with non-rheumatoid eye inflammation. A significant difference was noted in the findings comparing rheumatoid and non-rheumatoid patients as regards haemoglobin and albumin/globulin ratio. The erythrocyte sedimentation rate was measured by two different methods but the readings in patients with rheumatoid disease were clearly far higher (Tables XIX*a*, *b*). It is interesting to note that the mean values for haemoglobin, erythrocyte sedimentation rate, and albumin/globulin ratio were all more abnormal in the patients with rheumatoid episcleritis and rheumatoid scleritis than in the rheumatoid control group, although only the findings for the erythrocyte sedimentation rate were statistically significant (Table XIX*c*).

The normal adult range for positive titres to *Toxoplasma gondii* is in the region of 30 to 40 per cent. Only the small group of patients with rheumatoid episcleritis had a figure that was very much higher (Table XX*a*). Beattie (1958) found 0·2 per cent of normal adults with a titre of 1/256 or more and Ludlam and Beattie (1963) reported only one titre at 1/512 in 478 women (0·2 per cent). In the patients with rheumatoid eye inflammation three of 35 patients (8·6 per cent) had titres of 1/256 or more. A similar increased incidence of high titres, noted in this paper in patients with rheumatoid eye inflammation, has been recorded in primary biliary cirrhosis (MacSween, 1973), reticulosis or after immunosuppressive or antimetabolite treatment (Broughton, 1970), pregnancy (Purtilo, Hallgren, and Yunis, 1972) and where a choroidoretinitis due to toxoplasmosis may relapse and toxoplasma antibody levels rise (Beattie, 1958). These are conditions associated with impaired cell-mediated immunity, and there is recent evidence of depression of cell-mediated immunity in some patients with rheumatoid arthritis (Waxman, Lockshin, Schnapp, and Doneson, 1973).

The titre of rheumatoid factor reflects the severity of the disease (Ziff, 1957; Kellgren and Ball, 1959) and the consequent prognosis (Duthie, Brown, Truelove, Barager, and Lawrie, 1964). It is not surprising, therefore, that some patients with rheumatoid episcleral or scleral inflammation had relatively high titres (Table XXII). Higher titres of rheumatoid factor are also associated with many extra-articular manifestations of rheumatoid disease such as subcutaneous nodules (Kellgren and Ball, 1959), vasculitis, peripheral neuropathy, and intractable skin ulcers (Epstein and Engleman, 1959). Autoantibody investigations in rheumatoid episcleritis and rheumatoid scleritis generally show results consistent with the expected incidence in a general rheumatoid population (Table XXI*a*). In tests of patients with rheumatoid arthritis, Pollak (1964) found that 24 per cent had positive antinuclear results, and Weir, Holborow, and Johnson (1961) found that 14 per cent were similarly positive. Thyroid antibodies in patients with rheumatoid eye inflammation showed no striking increase and indeed did not match the incidence of 15 of 62 cases (24·2 per cent) of rheumatoid arthritis found by Anderson, Goudie, Gray, and Buchanan (1961). The incidence of thyroid microsomal antibody in the present study of rheumatoid patients with eye inflammation is only slightly lower than that in the female group reported by Buchanan, Crooks, Alexander, Koutras, Wayne, and Gray (1961), where 26·1 per cent of 46 women had thyroid microsomal antibody. Johnson, Holborow, and Glynn (1965) found an incidence of smooth-muscle antibody in 6·4 per cent of 47 patients with rheumatoid arthritis and Doniach, Roitt, Walker, and Sherlock (1966) an incidence of 16 per cent in 32 patients with rheumatoid arthritis. The figure given here in rheumatoid scleritis (23·5 per cent) is slightly higher than in these two series, but it is difficult to reach any conclusion at this stage regarding this finding. High incidences of smooth-muscle antibody have been found in liver disease, particularly active chronic hepatitis (67 per cent), primary biliary cirrhosis (50 per cent), and cryptogenic cirrhosis (28 per cent) (Doniach and others, 1966). Certainly liver disease has been noted in association with rheumatoid arthritis, but the incidence was small; 0·66 per cent of patients with rheumatoid arthritis alone and 1·5 per cent of patients with Sjögren's syndrome, in whom the connective-tissue disorder was rheumatoid arthritis (Whaley and others, 1970). Salivary duct antibody was found in one-quarter of patients with rheumatoid arthritis, apparently uncomplicated by Sjögren's syndrome (MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson, 1967), and it would appear that the present findings are consistent with their observations without drawing any conclusion from the higher percentage of antibodies in the very small group with rheumatoid episcleritis. Armstrong (1967) considered that there was no evidence that gastric parietal-cell antibodies occurred more commonly in rheumatoid arthritis. In his investigation of patients with rheumatoid arthritis, 16·2 per cent of 246 females and 6·3 per cent of 79 males had positive results for gastric parietal-cell antibody. The small group of patients with rheumatoid episcleritis precludes any accurate conclusion and the group of patients with rheumatoid scleritis had a percentage incidence of gastric parietal-cell antibody of 16·2 per cent.

The results of the autoantibody tests in patients with episcleritis and scleritis, but with no clinical or radiological evidence of rheumatoid arthritis, are of particular interest (Table XXI*b*). One-third of the patients with scleritis gave positive results to tests for rheumatoid factor, and this might be an early manifestation of rheumatoid disease. Alternatively, it is conceivable that plasma cells in the scleral infiltrate could produce rheumatoid factor. It is known that plasma cells in the lymphoid tissues and in lymphoid infiltrates of synovium induce rheumatoid factor which then circulates in the blood stream (Mellors, Nowoslawski, and Korngold, 1961). It is possible, therefore, that the low titre of rheumatoid factor in the blood of those patients with scleritis, but no rheumatoid arthritis, merely reflects local scleral inflammation. However, only careful long-term follow-up studies will answer this question. The incidence of antinuclear factor in the serum of patients with non-rheumatoid scleritis could also indicate potential systemic disorder. Previous studies give a lower figure for the presence of antinuclear factor in the serum of patients with rheumatoid arthritis (14 per cent: Weir and others, 1961; 24 per cent: Pollak, 1964) and it is known that the prevalence and titre of antinuclear factor is highest in patients with severe arthritis (Hall, Bardawil, Bayles, Mednis, and Galins, 1960), vascular and granulomatous complications and Felty's syndrome (Alexander, Bremner, and Duthie, 1960; Ward, Johnson, and Holborow, 1964). Thyroglobulin antibody in patients with non-rheumatoid episcleritis and non-rheumatoid scleritis shows no increase beyond figures previously recorded for normal populations (5 per cent: Roitt and Doniach, 1958; 6 per cent: Owen and Smart, 1958; 4 per cent: Blizzard, Hamwi, Skillman, and Wheeler, 1959; 10 per cent: Beutner and Witebsky, 1962). Similarly, the incidence of thyroid microsomal antibodies is similar to the figure of 8 per cent given by Beutner and Witebsky (1962) for a normal population. Other autoantibody tests in patients with non-rheumatoid eye inflammation show little variation from general population studies for smooth-muscle antibody (13·5 per cent: MacSween, 1973) and gastric parietal-cell antibody, in which a general population study of hospital inpatients older than 50 years gave a figure of 10 per cent with the higher figure of 13·6 per cent in women (Anderson, Buchanan, and Goudie, 1967). MacSween (1973) in his group of 114 control patients in a study of primary biliary cirrhosis found an incidence of 10 per cent in women and 5 per cent in men.

The complement system consists of a group of serum proteins which amplify the effects of some antigen-antibody interactions (Austen, 1972). In rheumatoid arthritis, serum complement levels have been found to be normal or slightly raised (Ellis and Felix-Davies, 1959) and also reduced (Mongan, Cass, Jacox, and Vaughan, 1969; Weinstein, Peters, Brown, and Bluestone, 1972). Six rheumatoid patients in this study show reduced values (Table XXIII*a*) and it may be that hypocomplementaemia reflects active vasculitis, as has been shown previously in rheumatoid arthritis (Mongan, Cass, Jacox, and Vaughan, 1969; Weinstein and others, 1972). Six of the patients with non-rheumatoid eye inflammation also had serum complement levels below 100 mg/100 ml (Table XXIII*b*) and it is difficult to suggest causes of this finding. One of these patients gave a history of gout and essential hypertension, and another had erythema nodosa. However, it should be noted that there is some dubiety as to what is the range of normal for serum complement readings. The normal mean value in this study was taken as 145 mg/100 ml (±22 mg/100 ml) (Shanbrom, Khoo, and Lou, 1967). Thompson (1972) found a mean value of 118 mg/100 ml (±26 mg/100 ml) in 66 healthy individuals.

Immunoglobulins IgG, IgA, and IgM show little variation from normal figures in either rheumatoid or non-rheumatoid eye inflammation.

MORTALITY

The mortality in rheumatoid patients with episcleral and scleral inflammation was soberingly high, 45·5 per cent (Table XXIV). Fifteen of 33 known cases of rheumatoid episcleritis or rheumatoid scleritis had died since examination, compared with six of 33 known rheumatoid control patients (18·2 per cent). A decreased life expectancy has been observed in rheumatoid arthritis (Reah, 1963) and the outlook and severity of the condition is always more grave in sero-positive disease (Duthie and others, 1964). Jones and Jayson (1973) found that five of their original 14 patients with rheumatoid scleritis had died within three years, a mortality of 36 per cent. Only 18·5 per cent of their 133 control patients had died during the same period. The figures for mortality suggest that the conclusion of Decker (1972) was accurate: 'death due solely to rheumatoid arthritis is rare indeed. When it occurs it is due to the extra-articular manifestations'.

TYPE I ALLERGY (ATOPY)

The simplest methods of screening patients for type I allergy are either to carry out a series of skin tests, as has been done here, or to measure the blood levels of IgE. A group of 23 patients, each patient with non-rheumatoid eye inflammation, failed to give any indication on skin testing of a higher incidence of atopy than would have been expected in the general population. The incidence is within the range found in controls during studies of type I allergy (Johansson, 1967). This finding in a small series suggests that any external factor which might predispose to the interpalpebral distribution of inflammation found in many patients with episcleritis (Lyne and Pitkeathly, 1968) (Table IX*b*) does not have its origin in a susceptibility to atopic disease.

In a recent publication reviewing ocular manifestations of rheumatic disorders, Henkind and Gold (1973) plead for the inclusion of examination by an ophthalmologist in the protocol for any prospective study of rheumatic disease. This study, which has anticipated their request by some years, attempts to collate the ocular manifestations of episcleritis and scleritis with the rheumatic disorders, in particular rheumatoid arthritis.

Conclusions

1. Episcleritis occurred in approximately two patients per 1000 with rheumatoid arthritis (0·17 per cent). Scleritis occurred in approximately seven patients per 1000 with rheumatoid arthritis (0·67 per cent). Rheumatoid arthritis is common in patients presenting with scleritis, in this series occurring in one-third of patients (33·3 per cent), but is less common in patients presenting with episcleritis, occurring in approximately one patient in 20 (5·7 per cent).
2. All patients with rheumatoid episcleritis, rheumatoid scleritis, and non-rheumatoid scleritis had a mean age in the sixth decade, and the disease was more prevalent in women; whereas patients with non-rheumatoid episcleritis had a mean age in the fifth decade and the disease occurred equally between the sexes.
3. Rheumatoid episcleritis and rheumatoid scleritis were associated with widespread systemic disease, particularly of the cardiovascular and respiratory systems.
4. The most common complaints in episcleritis and scleritis were of redness and pain. Ocular pain was more evident in scleritis. Eye symptoms were more readily noted in non-rheumatoid inflammation.
5. All groups of patients had a very wide range in the duration of intermittent ocular inflammation, from a few days or weeks to 15 years or more.
6. Visual acuity is more severely depressed in scleritis than in episcleritis as a result of the associated ocular complications.
7. In a classification of scleritis as nodular,

diffuse, and necrotizing, diffuse scleritis was the most common form in both rheumatoid and non-rheumatoid scleritic inflammation. Posterior scleritis was more common in rheumatoid scleritis than in non-rheumatoid inflammation. Scleral translucency was found considerably more often in rheumatoid than in non-rheumatoid scleritis.

8. Ocular inflammation in episcleritis usually affected the interpalpebral area. Rheumatoid scleritis had a fairly even distribution in all four quadrants of the anterior sclera.
9. Episcleritis and scleritis associated with rheumatoid disease had more associated ocular complications than episcleritis and scleritis unassociated with rheumatoid disease.
10. Posterior subcapsular cataract was common in rheumatoid scleritis in cases in which the patient had been given systemic corticosteroids, occurring in 36 per cent of these patients.
11. Rheumatoid episcleritis and rheumatoid scleritis generally presented in patients with rheumatoid disease of long duration and in patients with radiological evidence of more advanced joint disease when compared with rheumatoid control patients.
12. Subcutaneous granulomatous nodules and skin atrophy were significantly more common in patients with rheumatoid episcleritis and rheumatoid scleritis when compared with rheumatoid control patients. Although not statistically significant, peripheral neuropathy, skin ulceration, skin bruising, and splenomegaly were all more apparent in patients with rheumatoid episcleritis and rheumatoid scleritis than in the rheumatoid control group.
13. Sjögren's syndrome was more evident in patients with rheumatoid episcleritis and rheumatoid scleritis when compared with general rheumatoid patients also referred to the Centre for Rheumatic Diseases.
14. The erythrocyte sedimentation rate was significantly higher in patients with rheumatoid episcleritis and rheumatoid scleritis when compared with the rheumatoid control patients.
15. Antibodies to *Toxoplasma gondii* in patients with rheumatoid episcleritis and rheumatoid scleritis showed a higher percentage of raised titres compared with studies in normal patients.
16. Autoantibody studies in patients with rheumatoid episcleritis and with rheumatoid scleritis showed little variation from results expected in rheumatoid arthritis. Autoantibody studies in patients with non-rheumatoid scleritis showed a high incidence of rheumatoid factor (33·3 per cent) and antinuclear factor (33·3 per cent).
17. The prognosis for life is poorer in patients with rheumatoid disease complicated by episcleritis or scleritis when compared with rheumatoid controls matched for age, sex, and year of presentation; 45·5 per cent of those with eye inflammation had died since the examination, compared with 18·2 per cent of the control group.
18. There is no clear evidence of any higher incidence of atopic disease in patients with non-rheumatoid episcleritis and non-rheumatoid scleritis as compared with the expected incidence in a general population.

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Tables VIII, XII, XVII, XVIII, XXIV, XXVII, XXVIII, are reproduced in whole or in part by kind permission of Churchill Livingstone, Edinburgh.

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Evaluation of eyes enucleated for scleritis

FREDERICK T. FRAUNFELDER* AND PETER G. WATSON
From the Scleritis Clinic, Moorfields Eye Hospital, and the Department of Pathology, Institute of Ophthalmology

Of all ocular diseases few are more painful or serious than scleritis but, as it is a fairly rare disease, most ophthalmologists have relatively little experience in its diagnosis and management.

For the past 10 years Moorfields Eye Hospital has held a weekly scleritis clinic in the hope that the data obtained might further the understanding of this disease. A review of 207 patients with scleritis shows that 27 per cent of those with necrotizing scleritis died from an associated systemic disease within five years of the onset of the ocular inflammation (Watson and Hayreh, 1976).

Method and material

It was therefore important to discover why eyes with scleritis had been removed, and, if treatment had been given, why it had failed.

A 10-year retrospective study of enucleated eyes in which a principal histologic diagnosis of scleritis had been made was undertaken. Altogether 30 eyes which fulfilled these criteria were sent from hospitals in all parts of Great Britain to the Department of Pathology, Institute of Ophthalmology, London, from January 1965 to January 1975. Each patient's record was sent to the authors for review, or a questionnaire was completed by the surgeon who had removed the eye. The data giving details of treatment were incomplete in five cases and these have been excluded from Table IV.

A similar review was undertaken by Sevel (1967) 10 years ago. This present study is of the same geographical area but it does not include any of Sevel's cases.

Classification

Clinically, several types of scleritis can be distinguished:

ANTERIOR SCLERITIS

A diffuse, nodular, necrotizing scleritis with surrounding inflammation, or necrotizing without surrounding inflammation (scleromalacia perforans).

POSTERIOR SCLERITIS

The diagnosis of posterior scleritis has in the past depended on the observation of an accompanying anterior scleritis, although we know that posterior scleritis can occur on its own. Cleary, Watson, McGill, and Hamilton (1975) have recently described the characteristic fluorescein angiographic changes and fundus appearances in this condition, and it may be that the diagnosis will now be made more frequently without the need to observe the signs of anterior scleritis.

In this study the referring surgeons did not use this clinical classification and patients were classified as having anterior or posterior scleritis according to the observed pathological features (Table I).

Diagnosis

The clinical diagnosis of scleritis was not made in 12 patients, 40 per cent of the total, although they had severe scleral disease histologically (Tables I and II). The diagnosis of an accompanying posterior scleritis was not made in any patient, although it was present in 13 (43 per cent). None of the patients in this series was found to have posterior scleritis alone (Table I).

Scleritis is easy to overlook and the condition should therefore be borne in mind in eyes which are inflamed and refractory to treatment, present with exudative detachments, or have pericorneal ulceration. The main physical sign which allows the diagnosis of scleritis to be made is scleral swelling. The severe pain and the accompanying secondary glaucoma often obscure the inflammation of the sclera which is the primary condition. Clinically glaucoma is rare unless the scleritis

Table I *Pathological diagnoses (30 patients)*

Necrogranulomatous scleritis	*Patients (no.)*
Anterior only	17
Anterior and posterior	13
Posterior only	0

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*Visiting Professor, University of Arkansas School of Medicine (sabbatical year)

Address for reprints: Peter G. Watson, 22 Parkside, Cambridge, England

Table II *Clinical diagnoses made in histologically confirmed scleritis (30 patients)*

Diagnoses	*Patients (no.)*
Anterior scleritis	12
Scleromalacia perforans	6
Malignant or absolute glaucoma	5
Endophthalmitis	2
Episcleritis	1
Mooren's ulcer	1
Lens-induced uveitis	1
Extraocular extension of ciliary body malignant melanoma	1
Inflammatory granuloma and staphyloma	1

involves the whole circumference of the globe.

Peripheral corneal guttering, or keratolysis associated with rheumatoid arthritis, can occur with or without scleritis and is often a further source of confusion. In five cases Mooren's ulcer was at one time diagnosed or suspected, although in Mooren's ulcer the accompanying inflammation is confined to the limbal area and does not extend into the sclera.

When we first analysed the results we thought there must have been some mistake and that the failure to diagnose scleritis in 40 per cent of patients was because we did not have sufficient information. It is almost certain, however, that the scleritis was was not recognized or considered to be of importance because seven of the 12 cases were not given steroids of any kind. In only one of the seven was there any contraindication for the use of steroids.

Age at enucleation

In this series there were more women than men (1·6:1)—almost the same as the ratio found in the large scleritis clinic series (Watson and Hayreh, 1976). The average age of patients at the time of enucleation was 67·8 years for women and 69·1 years for men (Figure). Many of these patients had had scleral disease for up to 30 years before losing the eye, which correlates with the finding that the average age of onset of necrotizing scleritis in patients seen in the scleritis clinic was 35 years. Sevel's series of 43 cases completed at the Institute of Ophthalmology from 1950 to 1964 had an average age of 63 years and a 1·75:1 ratio of women to men (Sevel, 1967).

It is not known why eyes with severe disease were enucleated five years later in this series than in that of Sevel, although increased steroid usage might have delayed the final outcome. Possibly enucleation is now being undertaken at a much later stage in the disease than it was 10 years ago.

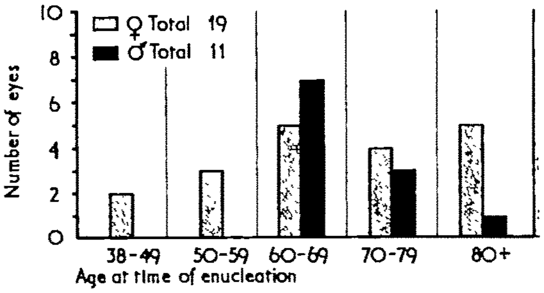

FIGURE *The average age of patients at the time of enucleation*

Reasons for enucleation

Pain was the reason for enucleation in 82 per cent of the patients (Table III). In two instances a diagnosis was made of endophthalmitis in functionless eyes; another had a massive staphyloma with impending perforation, and a further patient had a small staphyloma resembling a malignant melanoma. In one case the patient died during surgery for repair of an ocular perforation and the eye was removed at necropsy; the eyes of patients who had Wegener's granulomatosis and periarteritis nodosa were also obtained at necropsy.

In a series of 207 patients with scleritis seen at Moorfields Eye Hospital during the same period, only three (1·5 per cent) came to enucleation, so it is rare indeed to enucleate an eye with scleritis. (Watson and Hayreh, 1976). Pain should not be a major problem since with adequate systemic or topical steroids it can be relieved. Possibly some eyes could have been salvaged if the patients themselves had returned for follow-up, or had

Table III *Reason for enucleation (30 patients)*

Reason for enucleation	*Patients (no.)*
Pain with loss of vision	23
Endophthalmitis	2
Large staphyloma	1
Malignant melanoma	1
Necropsy	
Died during ocular surgery for repair of perforation	1
Wegener's granulomatosis	1
Periarteritis nodosa	1

(Perforation of the eye was not given as a reason for enucleation) been able to tolerate adequate steroid treatment. It is well known that patients with severe chronic disease do not readily take their medication or attend for follow-up (Maddock, 1967); scleromalacia perforans occurs without inflammation and the patient does not attend until it is too late.

Perforation

In 11 of 30 cases (37 per cent) the eyes perforated before they were enucleated.

Sevel (1967) pointed out that the clinical diagnosis of perforation cannot always be confirmed histologically, since a thin residual layer of sclera may become transparent by dehydration, thus simulating perforation. An incidence of histologically confirmed perforation in this series of 11, or 37 per cent, is comparable to his series. Yet, on the pathology request slip or in the clinical record only once was a massive perforation with a staphyloma given as the reason for enucleation. In our experience staphylomas rarely perforate, except in cases with raised intraocular pressure with or without trauma, and if they should they can be managed surgically.

Effect of treatment

This study was partly initiated to see if subconjunctival steroid injections predisposed to scleral perforation. In the six patients who did not receive any steroids, none perforated, while 11 of 19 (nine of 14 topical and/or systemic, two of five subconjunctival) who were on some form of steroid treatment did perforate (Table IV). These data are, however, insufficient to differentiate which form of steroid delivery was more often associated with scleral perforation. Investigators have suggested that subconjunctival atropine (Tooker, 1931; Swan, 1951) or steroids (Sevel and Abramson, 1972; Watson, 1974) may cause a necrogranulomatous scleritis. Although the evidence is circumstantial, Sevel found the incidence of corneal perforation to be the same in those cases in which eyes had been enucleated before the general introduction of steroids, as afterwards. There has been a proper reluctance to give adequate suppressive dosages of steroids in the past, so that the disease has been allowed to progress. The dangers of allowing the disease to progress have to be weighed against the difficulties of long-term steroid treatment. Apart from the well known complications of cushingoid changes, hypertension, glaucoma, and cataract formation, steroids in fluctuating doses, have produced vasculitis in patients with rheumatoid arthritis (Hazleman, personal communication) and inhibited collagen formation in healing wounds (Ashton and Cook, 1951); they have also been shown to produce corneal perforation in non-infectious corneal disease (Brown, Weller, and Vidric, 1970). However, these drugs have suppressed the initiating stimulus and reversed the collagen destruction in scleritis associated with connective tissue disease (Ashton and Hobbs, 1952). Because of this, steroids have become standard treatment in the severest cases of scleritis and need to be used at near maximum dosages to control exacerbations. Once the disease is controlled, the dosage can be gradually reduced to a low maintenance level. This regimen may need to be repeated many times over a 30 to 50-year span in many unfortunate patients.

Table IV *Method of steroid delivery and incidence of ocular perforation (25 patients)*

Steroids	*Cases (no.)*	*Ocular perforation (no.)*	*Percentage*
None	6	0	0
Topical or systemic	14	9	57
Subconjunctival injection	5	2	40

Other changes found in the enucleated eyes

Eyes enucleated for scleritis showed a high incidence of other ocular disease (Table II). Uveitis, primarily anterior, was the most common complication and occurred in 68 per cent of cases. Glaucoma, which occurred in 46 per cent, was often severe and frequently associated with peripheral anterior synechiae. Three of these patients also had a retinal vein or artery occlusion. Retinal disease was found in 46 per cent and included non-rhegmatogenous retinal detachments (21 per cent), chorioretinitis, macular oedema, and macular degeneration. Six patients had intravitreal or suprachoroidal haemorrhages. Rubeosis, corneal ulcers, and des cemetoceles were seen in each of three patients.

This high complication rate of scleritis was not unexpected, although uveitis and glaucoma were seen more frequently in this series than in the scleritis clinic (Watson and Hayreh, 1976). In this series 68 per cent had uveitis as opposed to 37 per cent in the clinic, and 46 per cent of the enucleated eyes showed glaucoma as opposed to 28 per cent in the clinic. This suggested that scleritis with uveitis and glaucoma was an ominous sign. The fact that 21 per cent of cases had intraocular haemorrhage and three eyes had vascular occlusion associated with scleritis was unexpected, since these complications are rarely seen clinically and might possibly have been related to the glaucoma. How many of the haemorrhages occurred during enucleation is not known. The incidence of retinal detachment and cataract was less than that found by Sevel (1967).

Summary

A series of 30 enucleated eyes, all of which had a primary histological diagnosis of scleritis, was analysed. The average age of patients at enucleation was 68 years; many of these patients had had the disease for more than 30 years. In 40 per cent the diagnosis of scleritis was unsuspected and was often masked by multiple complications. Scleritis with uveitis and glaucoma was the most common combination to come to enucleation. In 82 per cent, pain was the reason for enucleation, which suggests that some patients were on inadequate levels of steroid treatment or were unable to tolerate them. In the series, 37 per cent of the eyes perforated. Perforation occurred in those patients who were having steroids but not in those who were not, but the data are inconclusive as to which method of steroid administration was most likely to cause ocular perforation.

The authors wish to acknowledge the help of Professor Norman Ashton for his advice and encouragement in the preparation of this paper, and also to thank Mrs Jane Field for obtaining records of patients throughout Great Britain.

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World Health Day
7 April 1976

FRANK W. LAW
London

The International Association for the Prevention of Blindness was an organization of long standing well known to all ophthalmologists. It issued a journal, its executive body met annually, and a General Assembly was held every four years at the time of the International Congress. Some had adverse views on its constitution; some were critical of its activities—or lack of them. In 1968, the President, Professor Franceschetti, died and, after a short period when the Association was under the Presidency of A. E. Maumenee, Gunnar von Bahr was elected President. He at once reorganized the Association, and the constitution and by-laws were completely revised. In Paris in May 1974, the General Assembly met, and fundamental changes were decided upon; these were necessary to embrace a more comprehensive range of powers, and institute legal machinery to hold and administer substantial funds of a multidisciplinary membership within which the main authority should rest with national delegations. Sir John Wilson, Director of the Royal Commonwealth Society for the Blind, was elected President, and Gunnar von Bahr Vice-President, his election ensuring liaison with the International Council. W. J. Holmes (USA) and W. S. Hunter (Canada) retained their offices of Secretary-General and Treasurer respectively. The organization was renamed the International Agency for the Prevention of Blindness, a happy change which, although retaining the old initials, indicated the difference between the old and the new organization.

The first meeting of the Executive Board was held in Puerto Rico in April 1975. Perhaps its most important action was the decision to establish national committees throughout the world; this has already been achieved in 42 countries, including our own. The Agency works in official relationship with the World Health Organization, UNICEF, and FAO and has contact with all related UN mechanisms. Under its new constitution, which came into force on 1 January 1975, the Agency represents a partnership between the organizations concerned internationally with ophthalmology and with the rehabilitation of the blind. This collaboration is reproduced at the national level with additional links with other scientific disciplines and community service organizations.

At the 28th World Health Assembly held in Geneva in May 1975, an important resolution was adopted, urging all governments to intensify action for the prevention of blindness and, on World Health Day (7 April 1976), to celebrate internationally the theme 'Foresight Prevents Blindness'. One of the chief objects of this communication was to draw attention to this important date.

The Priorities and Projects Committee of the Agency met in Washington in November 1975, and this country was represented by Michael Roper-Hall, chairman of the group on ocular trauma. The British National Committee for the Prevention of Blindness is this country's link with the Agency and consists of representatives of the organizations concerned nationally with blindness and its prevention and of the responsible government departments. Two subcommittees are charged with a national campaign of fund raising (probably to be concentrated annually into a prevention of blindness week) and with the formulation of priorities for national and international action.

There is no need to list for ophthalmologists the principal causes of blindness and their distribution and incidence, nor to recite the formidable statistics of world blindness. One may be allowed, however, to submit the above record, and to ask all to keep informed of developments, and to lend support to the campaign, especially in relation to World Health Day.

A report on mobilization of resources submitted to the Executive Board at Puerto Rico ended thus: 'Our objective is this: In every donor country during 1976 that every family should be asked—in thanksgiving for sight—to give $10 to save the sight of its fellow countrymen or of the millions in the third world. If we can raise this campaign to that degree of universal appeal, the result could be spectacular'.

Information about the Agency and about the British National Committee can be obtained from the International Agency for the Prevention of Blindness, Commonwealth House, Haywards Heath, Sussex RH16 3AZ, England.

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Book reviews

Advances in Ophthalmology, vol 31, Treatment of Retinoblastomata. Edited by E. B. STREIFF, M. SAUTTER, and M. J. ROPER-HALL. 1975. Pp. 240, 93 figs, 17 tables, refs. Karger, Basel (DM132)

This volume is the latest in a continuing series on contemporary ophthalmic subjects. Four chapters are concerned with retinoblastoma, the morphology of the corneal endothelium, the non-visual control of ocular movements, and the reaction of the retina to intensive light.

The discussion on retinoblastoma by Bedford reviews current ideas on the natural history and management of these tumours, and the author concludes with a summary of his recommended therapeutic regime for different types of presentation.

The remaining three articles are in German, one sadly without an English summary. Schierhölter and Honegger present some of their work on corneal endothelium under physiological conditions and after mechanical damage, and the morphological changes occurring in regenerating endothelial cells are described in detail with excellent illustrations. The physiology of the non-visual control of eye movements is discussed by Korner with a presentation of experimental data on saccadic movements in human subjects and optokinetic responses in animals. Finally, Wallow and his co-workers describe the effects of intense light from argon and helium lasers and the xenon arc photocoagulator on the retinae of experimental animals. The ophthalmoscopic and histological threshold doses are correlated, and an attempt is made to relate tissue damage to loss of function. Using this information certain safety thresholds are suggested for man for intense light in the visible spectrum.

The four articles are fully representative of the high standards set by the editors in this series of volumes. But once again this policy of multilingual presentations that characterizes *Advances in Ophthalmology* must be criticized. The average English ophthalmologist does not have a working knowledge of technical German and therefore only one of the four articles in this volume will be informative, and at a cost of over £20 that is a high price to pay even in these inflationary times.

T. J. FFYTCHE

Color in Business, Science and Industry, 3rd ed. By D. B. JUDD and G. WYSZECKI. 1975. Pp. 553, figs, tables, refs. Wiley, Chichester (£15)

When the late Deane Judd first published this book 23 years ago it was something of a landmark. Dr G. Wyszecki became his partner for the second edition, and has now had to shepherd the third through the press on his own, and is looking to the need for a fourth 'in about 10 years' time'.

The material has been brought up to date in a competent and relaxed manner, the latter being particularly commendable in a topic frequently as dry as colorimetry. There are many new and helpful illustrations, but some of the older ones were old even in the first edition, and Chapter 1 could do with a new look. This edition more than the earlier ones, attempts to come to grips with fundamentals and offers much useful information on relatively new fields, such as colour television. The reader will find that the approach is very much that of a physicist; for instance it overlooks that if an older person is exposed to Standard Illuminant C the visual effect may be the same as that of Standard Illuminant B on a younger person: the conclusion that extraocular standards are of limited value remains to be drawn. Apart from such small details the new edition enhances the authority of the earlier ones as a standard work in this abstruse field, and can be recommended without reservation both as a text and as a source book.

R. A. WEALE

Diabetic Microangiopathy: Its Development Based on New Knowledge on Capillary Tissue Oxygen Delivery and its Possible Prophylaxis. Edited by J. DITZEL and J. E. POULSEN. 1975. Pp. 83, figs, tables, refs. (Supplement to *Acta med. scand.*) (£4·50)

This book is a collection of papers given at a symposium in Aalborg, Denmark, commemorating the 100th anniversary of the birth of August Krogh. Krogh, the 1920 Nobel prizewinner in medicine and physiology for his work on the physiology of capillaries, became acquainted with Best's and Banting's researches on insulin during his visit to Toronto in 1922, and on his return to Denmark, he pioneered the development and production of the hormone.

Of the eight papers contained in the book the last three, by Jorn Ditzel and Eberhard Standl on problems of tissue oxygenation in diabetes, live up to the outstanding tradition of their compatriot. They lead the reader through the intricate cytological and enzymatic complexities of diabetic microangiopathy with unswerving lucidity. The problems of blood flow volume, viscosity, erythrocyte oxygen binding capacity, haemoglobin variations, and changes in glycolytic processes in the retina which depend on the phosphate levels in the blood, are just a few problems considered and beautifully explained. Ditzel's 'three in one' hypothesis on the mechanisms of diabetic retinopathy revolves round the role of phosphorus ions in production of 2-3 diphospho glycerate by the erythrocyte which in turn regulates the affiliation of oxygen to haemoglobin. The increase of 2-3 diphospho glycerate enhances the oxygen availability to the hypoxic diabetic retina. If giving phosphate dietary supplement to young diabetics will prevent or influence development of retinopathy has yet to be proved, the exposition in bringing forward a fascinating array of information marshalled in such a way that is bound to stimulate ophthalmologists concerned with diabetic retinopathy will confront these concepts with their own ideas heavily influenced by information from fluorescein angiography. While the authors discuss the delicate minutiae of capillary-tissue oxygen delivery systems, in a strange way the crudities of photocoagulation therapy, inflicted on the diabetic retina by the clinician, may seem less embarrassing and more logical.

The other five papers are on the impact of August Krogh on the insulin treatment of diabetes and our present status (Poulsen), autoregulation of the microcirculation (Crone), blood oxygen transport system (Garby), the ophthalmoscopic and fluorescein angiographic picture of diabetic retinopathy (Larsen), and dynamic changes in the microcirculation of diabetics as related to diabetic microangiopathy (Kohner).

They are competent and informative reviews and the book as a whole is very much worth reading.

R. RUBINSTEIN

XIth ISCERG Symposium, Bad Nauheim 1973 (Documenta Ophthalmologica Proceedings Series, vol. 4). Edited by E. Dodt and J. T. Pearlman. 1974. Pp. 518, 293 figs, tables, refs. Junk, The Hague (DG150)

This collection of papers from the annual symposium reflects the continuing development of visual electrophysiology. Founded to provide a forum for research workers and clinicians interested in electro-retinography it has assimilated newer techniques of retinal and cerebral studies. The increasing importance of the visually-evoked response is reflected in the number of papers.

The standard of the contributions is variable. This is because in order to attend the symposium the delegate has to present a paper and it has been the society's policy to publish all such contributions. The official language is English and many of the translated papers are less than fluent.

The result is a useful review of this rapidly developing field. The book will be of value to both clinicians and research workers involved in visual electrophysiology but it will be of little interest to most ophthalmologists.

J. H. KELSEY

The Eye in General Practice, 7th ed. By C. R. S. Jackson, 1975. Pp. 174, 47 figs. Churchill Livingstone, Edinburgh and London (£5·00)

That this book should now have reached its seventh edition shows how useful it is for practitioners. It is also an excellent book for the medical student, being of convenient size, beautifully produced and illustrated, clearly written, and it has a well chosen and balanced content.

As is always the case with revision some new material has been added and other chapters have been modified while a few nostalgic hints of its past still linger—such as, the advice to the general practitioner to paint the conjunctiva with 1 per cent silver nitrate in cases of conjunctivitis which have lasted several days, and if an eye is red and irritable from a foreign body to instil atropine, advice which the author clearly does not like giving, as having given it he promptly says 'it should be avoided if possible'.

There are one or two minor points on which a future edition might perhaps with advantage be slightly altered, such as the advice to the general practitioner to pass a fine probe into the lacrimal passages in cases of injury near the inner canthus: this seems rather much for the average general practitioner to take on. Another is the slightly irritating repetition, at the foot of the first page of every chapter in part one, of reference to the fact that a drawing of the whole eye is given in Fig. 1. A third point the author might consider looking at for future editions is the rather stereotyped and surely obsolete implication that macular degeneration is due to arteriosclerosis.

I very much liked the optical diagrams, and admired the poetic licence in the illustration of diplopia. Altogether I found this book very good value and highly recommend it.

REDMOND SMITH

First International Symposium on Artificial Lens Implantation (Documenta Ophthalmologica Proceedings Series, vol. 6). Edited by A. T. M. van Balen. 1975. Pp. 169, figs, tables, refs. Junk, The Hague (DG55)

This symposium was held at Utrecht in April 1974, but of course there has been an active 'intraocular implant club' in existence for more than 10 years.

The papers cover nearly all aspects of iris-clip lenses, and I would particularly recommend interested readers to start with the 'Discussion' where they will find some abrasive and helpful argument on such problems as the cause of macular oedema, the indications of iris-clip implant in children, and the management of complications.

Those of us who are familiar with this technique of cataract surgery know how valuable it is to the patient, and the number of surgical centres up and down the country, and indeed throughout the world, which are producing good results, increases every year.

Undoubtedly, the results in senile cataracts are the best, and there are few contraindications to the use of iris-clip lens. The results in children with congenital cataract, however, are disappointing. Binkhorst, who has had 20 years' experience in this field, confines his operation to those who have bilateral incomplete forms of cataract, and then to the worse eye only. Good visual results are obtained in traumatic cases over the age of five years, and in this group the implant appears to be superior to a contact lens.

An interesting trend back to an extracapsular technique is discussed, and Binkhorst recommends a one-stage operation with a capsular supported lens. It is suggested that this gives a better immobilization of the implant and reduces the incidence of macular oedema to below that of all forms of intracapsular extractions. Statistical proof of this is not yet available. Those in a position to use phako-emulsification on their patients also claim that an irido-capsular implant has a very low rate of complications.

A useful book, then, for anyone who wants to find out about lens implant surgery, and a 'must' for the converted.

N. DALLAS

Ophthalmic Pathology of Animals: An atlas and reference book. By L. Z. SAUNDERS and L. F. RUBIN. 1975. Pp. 258, 27 figs, 30 plates, refs. Karger, Basel (DM155)

The writing of this book has clearly been a labour of love, the result being an exquisitely produced conspectus of what is known about the pathology of eye diseases in lower animals. The text is brief but to the point, with a stimulating introduction to the historical tradition in which veterinary ophthalmology stands, and it is accompanied by a superb selection of photomicrographs on high grade glossy paper. As the authors explain in their preface, the text is basically descriptive, with no serious attempt to discuss pathogenesis, although mention of each disease entity is followed by appropriate references to which the reader can refer for further information. This eminently readable book can be recommended to anyone seeking an authoritative and reasonably comprehensive account of the histopathological findings in veterinary ophthalmology. The only reason it might fail to achieve the authors' ambition of arousing wider interest in this fascinating branch of comparative ophthalmology, is that its high cost is likely to deter all but established devotees from adding it to their libraries—and that would be a pity. A. GARNER

Recent Advances in Ophthalmology, vol. 5. Edited by P. D. TREVOR-ROPER. 1975. Pp. 319, figs, tables, refs. Churchill Livingstone, Edinburgh (£9·50)

This is essentially a review of recent contributions to our knowledge and the editor has chosen 12 disciples to expound their particular interest. Each chapter is a complete story in itself, well told, illustrated with discretion, with a useful bibliography. The standard of presentation is well sustained and it is impossible to provide the reader with an overall view of expectation without enumerating the subjects discussed and their authorship. They are as follows: Electrophysiology of the eye (N. R. Galloway), Ocular motility (Ian Strachan), Corneal grafting (T. A. Casey), Cataract extraction (Dermot Pierse), Glaucoma (A. R. Elkington), The macula (T. J. ffytche), Surgery of retinal detachment (M. G. Glasspool), The eye in thyroid disease (A. L. Crombie), Inherited metabolic disorders and their ophthalmic manifestations (Brian Harcourt), Connective-tissue disorders and the eye (P. G. Watson), Adverse drug reactions (Sidney I. Davidson), Contact lens (H. Jonathan Kersley).

This is an ideal size of medical text for the ophthalmologist in harness who wishes to keep up with modern thought. It is a book to be enjoyed and kept handy for reference. Some of its chapters are so well written as to make a second reading an added pleasure. For those who have not made a purchase there is a treat in store. In many ways they are to be envied. S. J. H. MILLER

System of Ophthalmology, vol. XIII, The Ocular Adnexa, Part I, Diseases of the Eyelids, Part II, Lacrimal, Orbital, and Para-orbital Disease. Edited by S. DUKE-ELDER. 1974. Pp. 1236, 1300 figs, refs. Kimpton, London (£25)

Part I comprises 592 pages on the ocular adnexa and is mainly concerned with diseases of the eyelids. Grouped into circulatory and secretory disorders, inflammations, dermatoses, systemic involvements, atrophies and hypertrophies, cysts and tumours, the field is well covered and profusely illustrated. The overriding impression on reading through its pages is the extraordinary ramification of the science of ophthalmology. A large section of this volume as might be expected is concerned with dermatology, but a glance at a chapter on the lids in systemic disease will persuade even the most surgically orientated that the medical aspects of ophthalmology form a subject of wide complexity and variety of interest.

Part II is on diseases of the lacrimal apparatus and of the orbit and para-orbit, a text of some 600 pages illustrated richly and accompanied by an astonishing bibliography. Sir Stewart and Peter Macfaul are to be congratulated on gathering together in two volumes, such an ordered compendium of syndromes as they affect the ocular adnexa. They invade the province of the nasal surgeon, of the neuro-surgeon, of the bacteriologist and parasitologist and if this were not enough, orbital involvement by general disease takes the reader into the camp of the endocrinologist and requires an understanding of the lipoidoses, necrotising angiitides and the osteopathies.

No library can afford to be without these two volumes. At £25·00 a time they are an excellent buy and an unfailing source of reference for the ophthalmologist in practice. S. J. H. MILLER

Obituary

Kathleen Long, FRCS, DOMS

Miss Kathleen Long, consultant ophthalmic surgeon to Northampton and Kettering hospital group, died on 5 February 1976. She was 58. She graduated MB, BS from Durham University in 1940 and after a period in general practice became Fellow of the Royal College of Surgeons, Edinburgh in 1945. During the next five years her interest in ophthalmology developed and in 1958 she was appointed to the Northampton and Kettering group of hospitals.

Miss Long kept herself up to date and was a frequent attender of ophthalmic conferences both here and overseas. In 1964 she suffered a ski-ing accident which led to an arthrodesis of her knee. Despite her handicap she carried on in a remarkably cheerful way until her sudden death in February.

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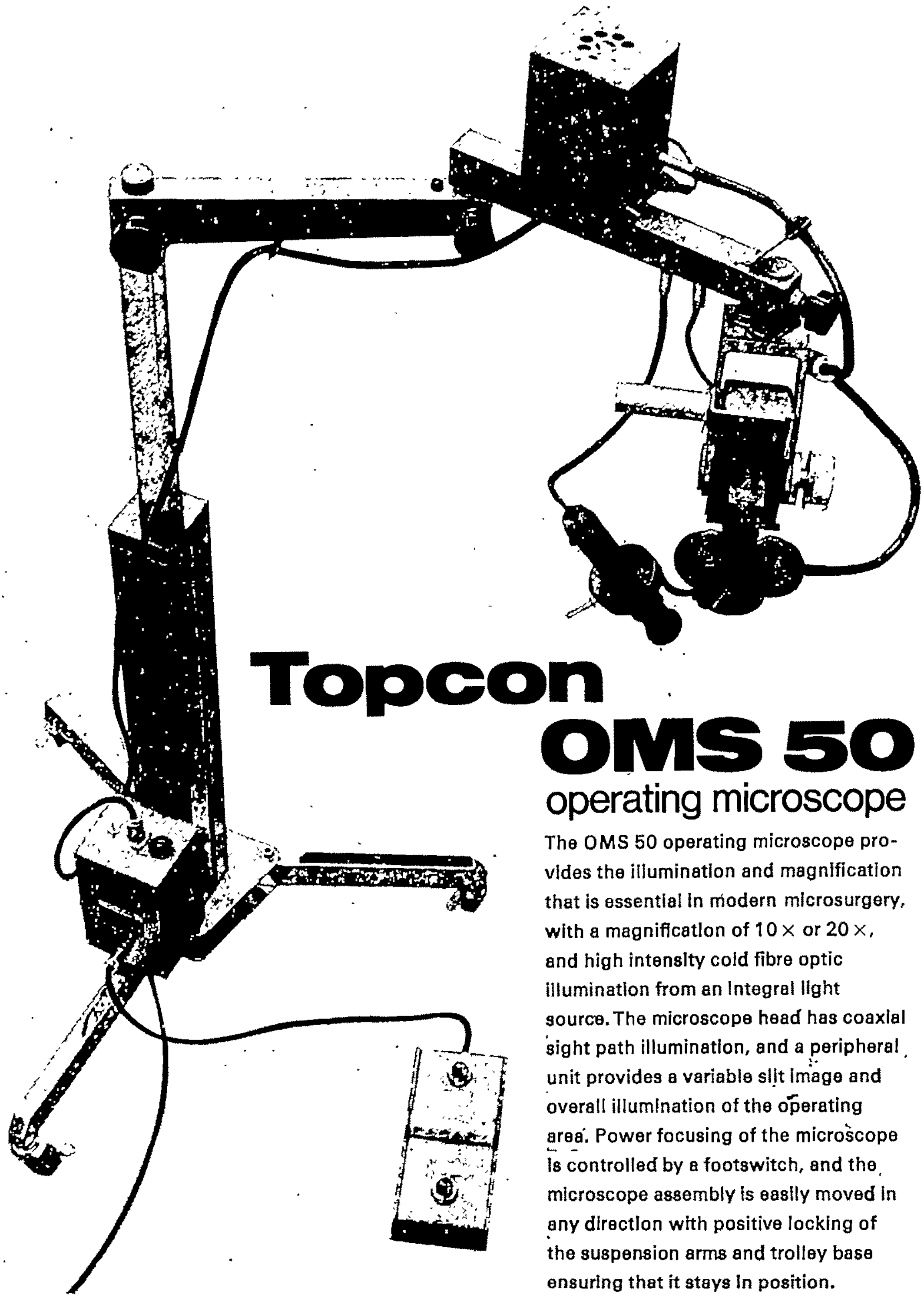

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CONTRIBUTORS

M. A. BEDFORD F.R.C.S.	Consultant Eye Surgeon, St. Bartholomew's Hospital, London; Consultant Surgeon, Moorfields Eye Hospital, London
C. D. BINKHORST, M.D.	Director of Ophthalmology, Hospital Group Zeeuwsch-Vlaanderen, Netherlands
J. E. CAIRNS, M.B., B.S., F.R.C.S.	Consultant Ophthalmic Surgeon, Addenbrooke's Hospital, Cambridge
T. A. CASEY M.Ch., F.R.C.S.	Consultant Ophthalmic Surgeon, Corneo-Plastic Unit and Eye Bank, Queen Victoria Hospital, East Grinstead, Sussex
G. V. CATFORD F.R.C.S., D.O.	Consultant Ophthalmic Surgeon, St. George's Hospital, London; The Royal Masonic Hospital, London; The Royal London Homeopathic Hospital
D. P. CHOYCE M.B., M.S.(Lond.), F.R.C.S.	Hunterian Professor, R.C.S., Senior Consultant, Regional Eye Centre, Southend General Hospital, Essex; Consultant Ophthalmologist, Hospital for Tropical Diseases, London
J. H. DOBREE, M.S.(Lond.), F.R.C.S.	Ophthalmic Surgeon, St. Bartholomew's Hospital and North Middlesex Hospital, London
IAN M. DUGUID M.D., Ph.D., F.R.C.S.	Consultant Surgeon, Moorfields Eye Hospital, London; Consultant Ophthalmic Surgeon, Westminster Hospital, London .
PETER FELLS, M.A., M.B., B.Chir., F.R.C.S., D.O.	Consultant Ophthalmologist and Director of the Orthoptic Department, Moorfields Eye Hospital, (City Road Branch), London; Senior Lecturer in Ophthalmology, Institute of Ophthalmology, University of London
Sir ALLEN GOLDSMITH K.C.V.O., M.B., F.R.C.S.	Emeritus Consultant Ophthalmic Surgeon, Middlesex and Royal National Orthopaedic Hospitals, London; Honorary Consultant Surgeon, Moorfields Eye Hospital, London
JAMES R. HUDSON C.B.E., M.B., B.S., F.R.C.S.	Surgeon, Moorfields Eye Hospital, London; Ophthalmic Surgeon, Guy's Hospital, London; Honorary Ophthalmic Surgeon, Hospital of St. John and St. Elizabeth, London; King Edward VII Hospital for Officers, London
P. A. M. LEONARD, M.D.	Ophthalmologist, University of Leyden, Netherlands
GLYN A. S. LLOYD M.A., D.M., F.R.C.R.	Teacher in Radiology, University of London; Consultant Radiologist, Moorfields Eye Hospital, London; Director, Department of Radiology, The Royal National Throat, Nose and Ear Hospital, London
CHARLES J. F. MAGUIRE M.B., B.Ch., F.R.C.S.	Ophthalmic Surgeon, Royal Victoria Hospital, Belfast
BRUCE MATHALONE F.R.C.S.(Eng.), F.R.C.S.(Ed.)	Consultant Ophthalmic Surgeon, Royal Eye Hospital and Kensington and Chelsea and Westminster A.H.A.(T.)
STEPHEN J. H. MILLER M.D., F.R.C.S.	Surgeon Oculist to Her Majesty the Queen; Ophthalmic Surgeon, St. George's Hospital, London and National Hospital, Queen Square, London
MARSHALL MILLER PARKS, M.D.	Ophthalmic Surgeon, Children's Hospital National Medical Centre, Washington
N.S.C. RICE M.D., B.Chir., F.R.C.S., D.O.	Consultant Ophthalmic Surgeon, Moorfields Eye Hospital and Senior Lecturer at the Institute of Ophthalmology, London
M. J. ROPER-HALL Ch. M., F.R.C.S.	Consultant Surgeon, Birmingham and Midland Eye Hospital; Consultant Ophthalmic Surgeon, United Birmingham Hospitals
JOHN R. SAMUEL F.F.A.R.C.S.(Eng.), D.A.	Consultant Anaesthetist, Moorfields Eye Hospital, London and St. Peter's Group of Hospitals, London
P. J. HOLMES SELLORS M.A., B.M., B.Ch.(Oxon.), F.R.C.S.	Surgeon Oculist to Her Majesty's Household; Consultant Ophthalmic Surgeon, St. George's Hospital, London
P. D. TREVOR-ROPER M.A., M.D.(Camb.), F.R.C.S.(Eng.)	Consultant Eye Surgeon, Westminster Hospital and Moorfields Eye Hospital, London
R. A. N. WELHAM M.B., F.R.C.S., D.O.	Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London and The Royal Berkshire Hospital, Reading
JOHN E. WRIGHT M.D., F.R.C.S., D.O.	Consultant Surgeon, Moorfields Eye Hospital, London; Consultant Ophthalmic Surgeon, The Royal National Throat, Nose and Ear Hospital, London
KENNETH WYBAR M.D., Ch.M., F.R.C.S.	Surgeon and Director, Orthoptic Department, Moorfields Eye Hospital, London; Ophthalmic Surgeon, The Hospital for Sick Children, Great Ormond Street, and Royal Marsden Hospital, London; Civilian Consultant in Ophthalmology to the Royal Navy

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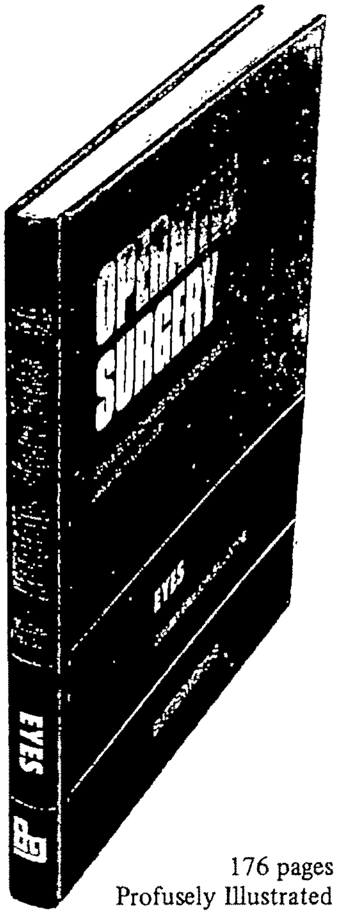

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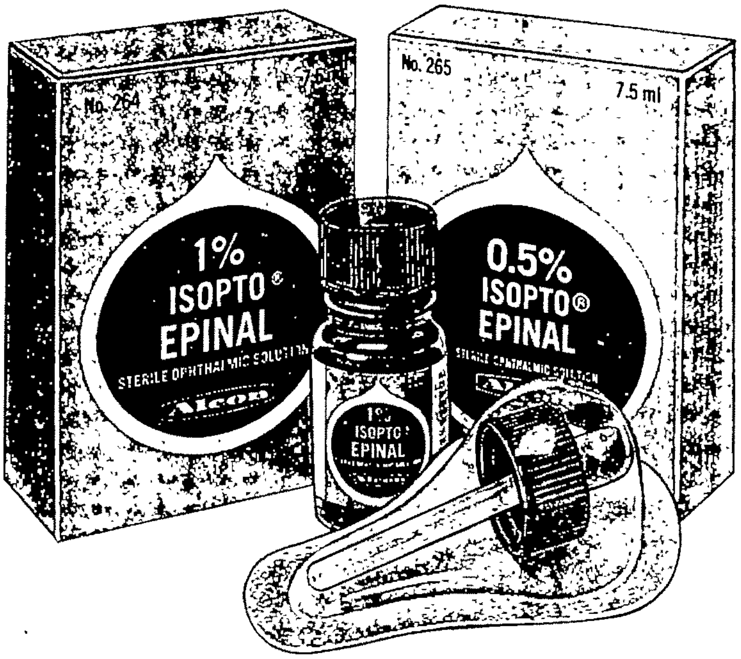

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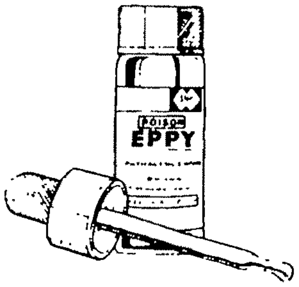

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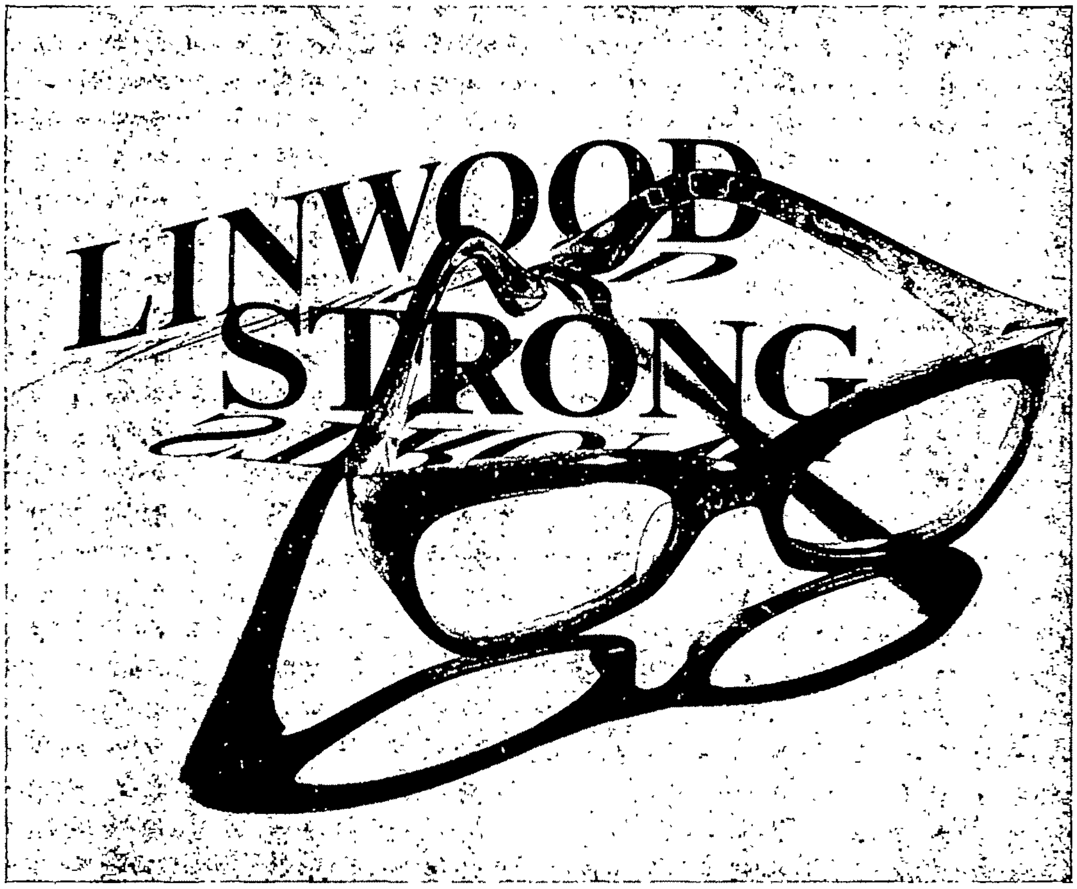

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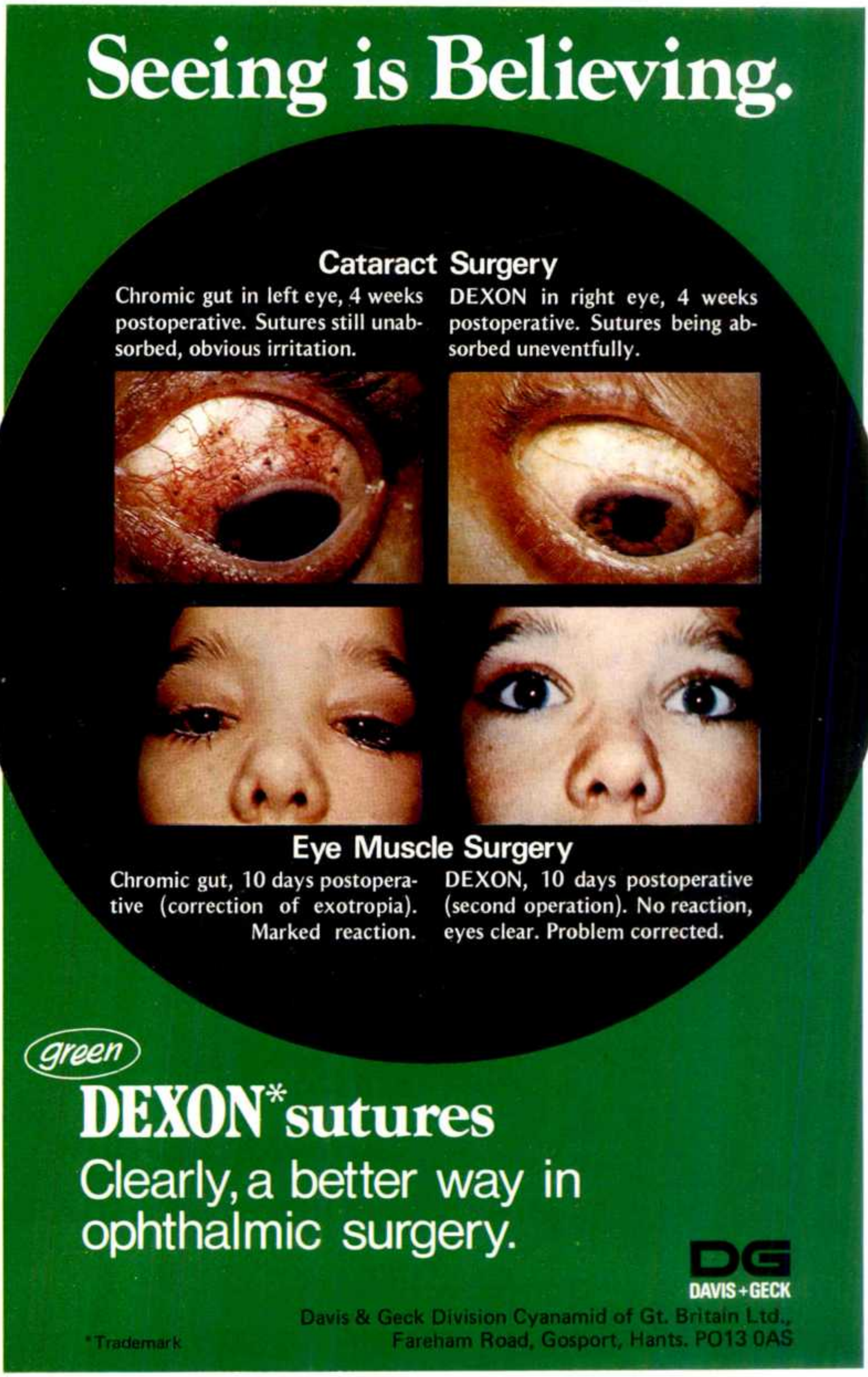

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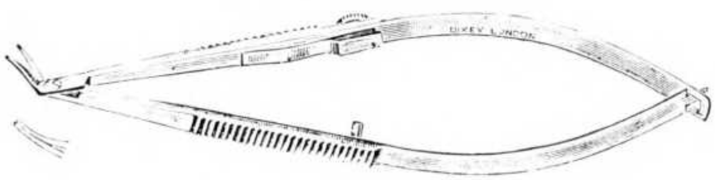

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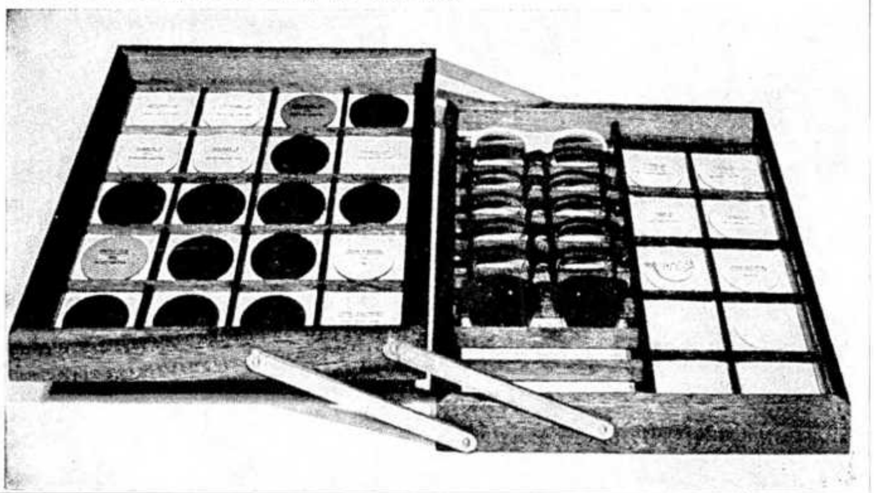

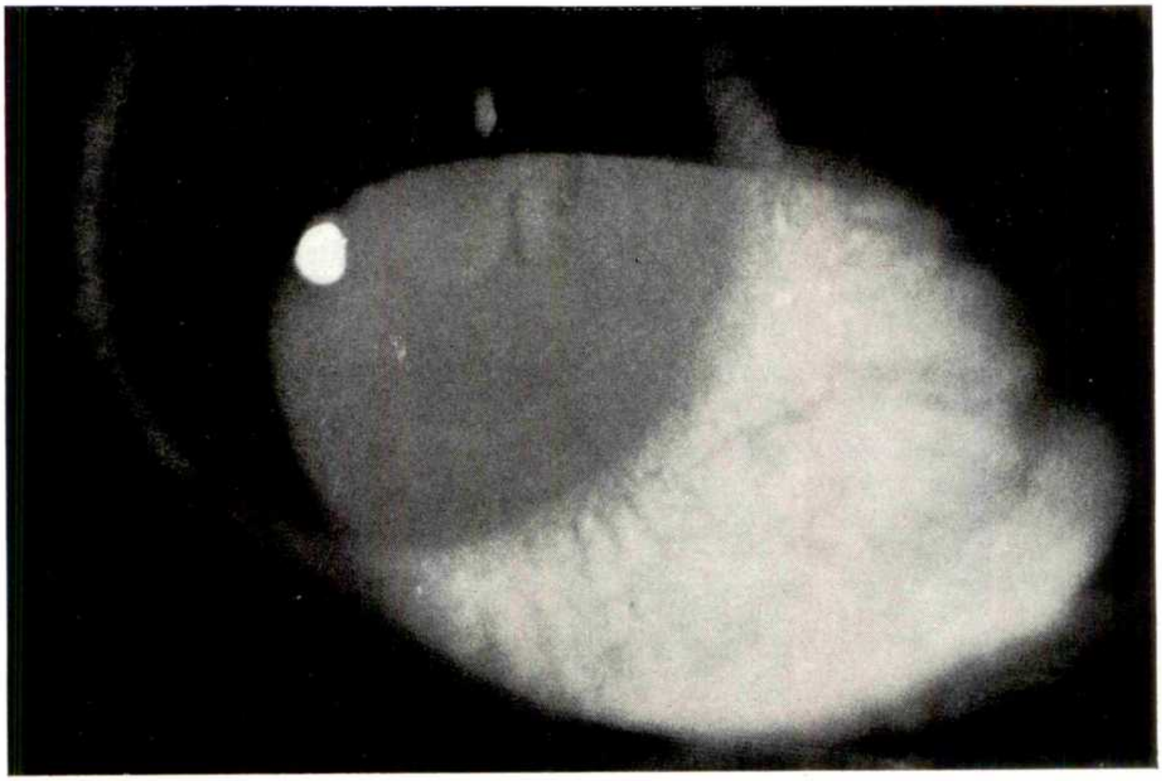

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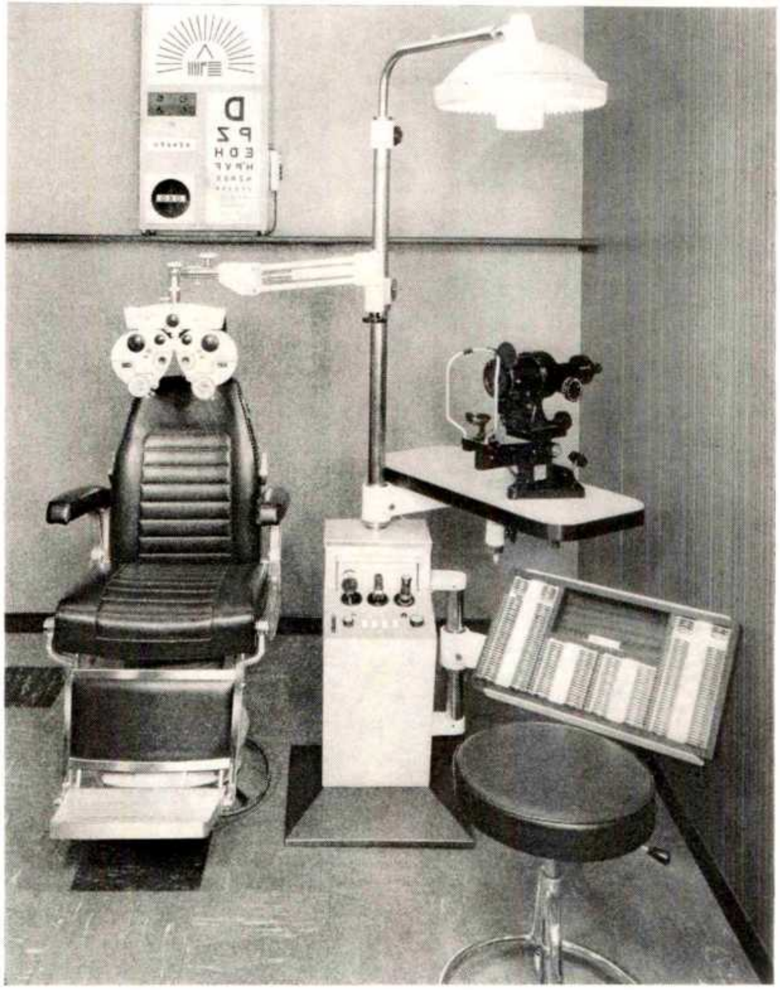

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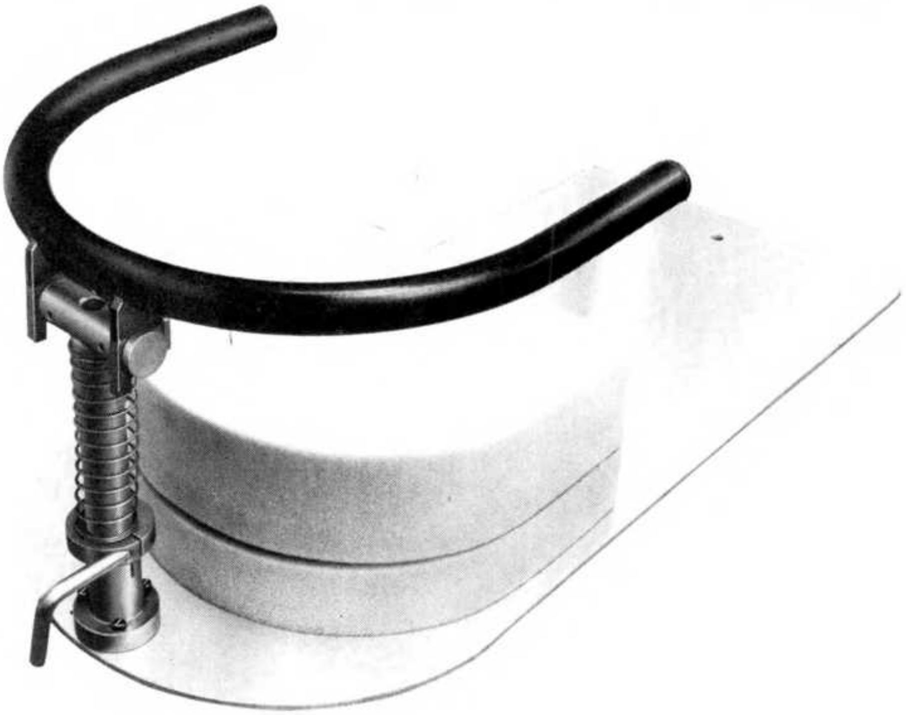

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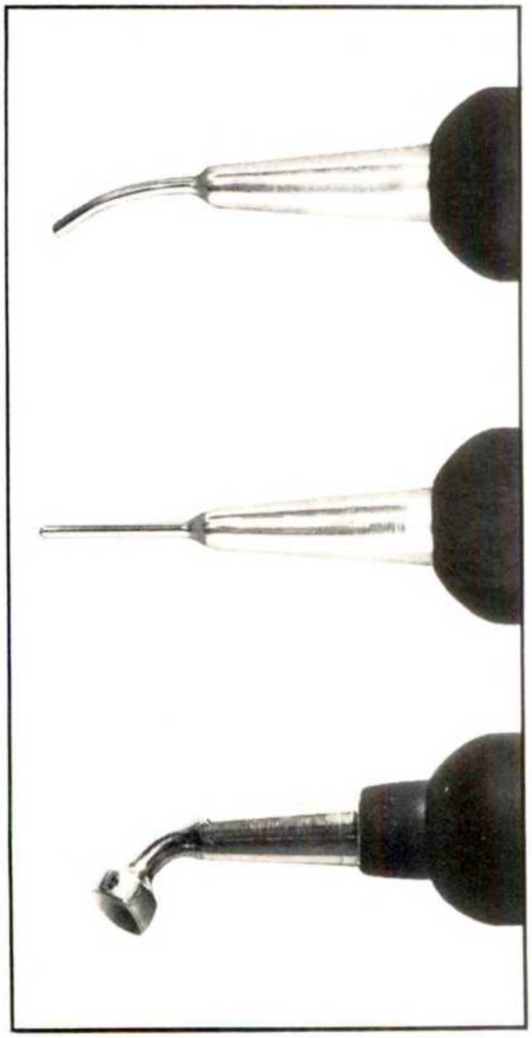

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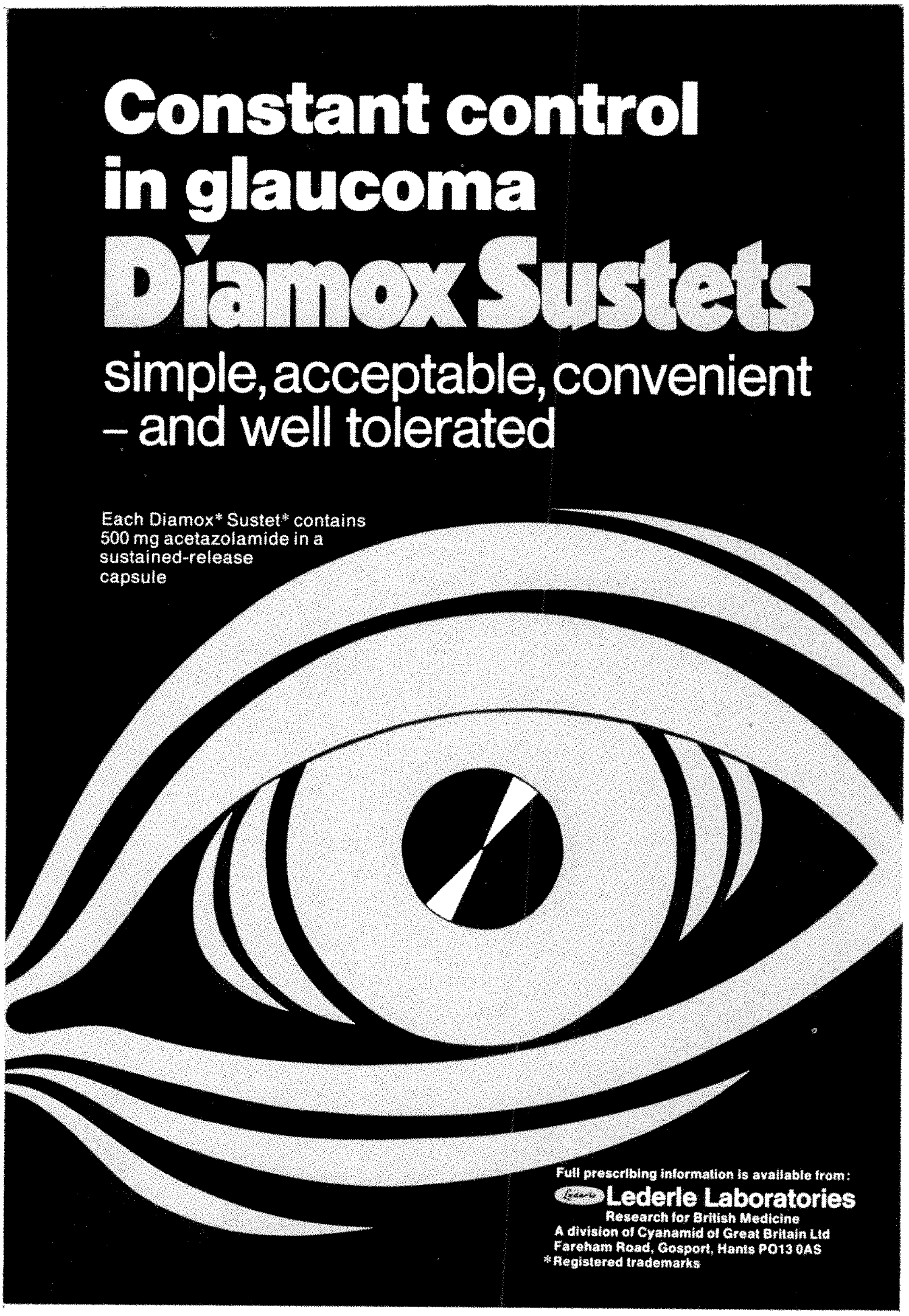

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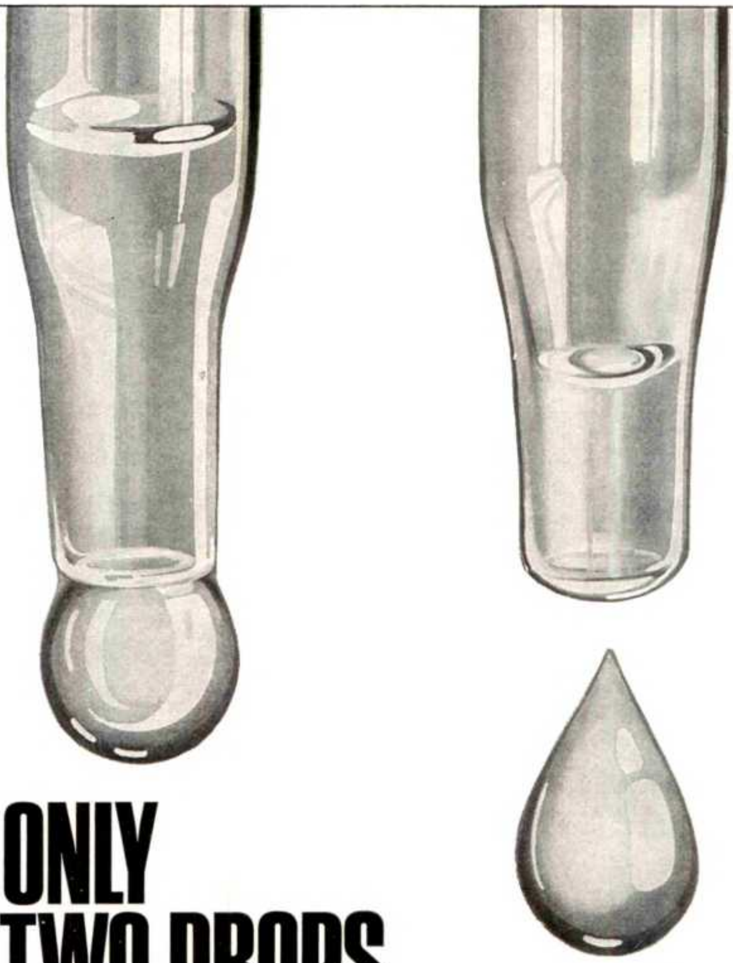

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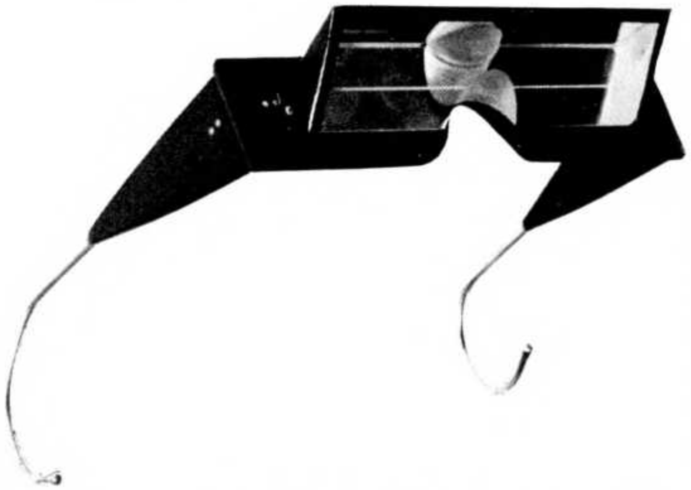

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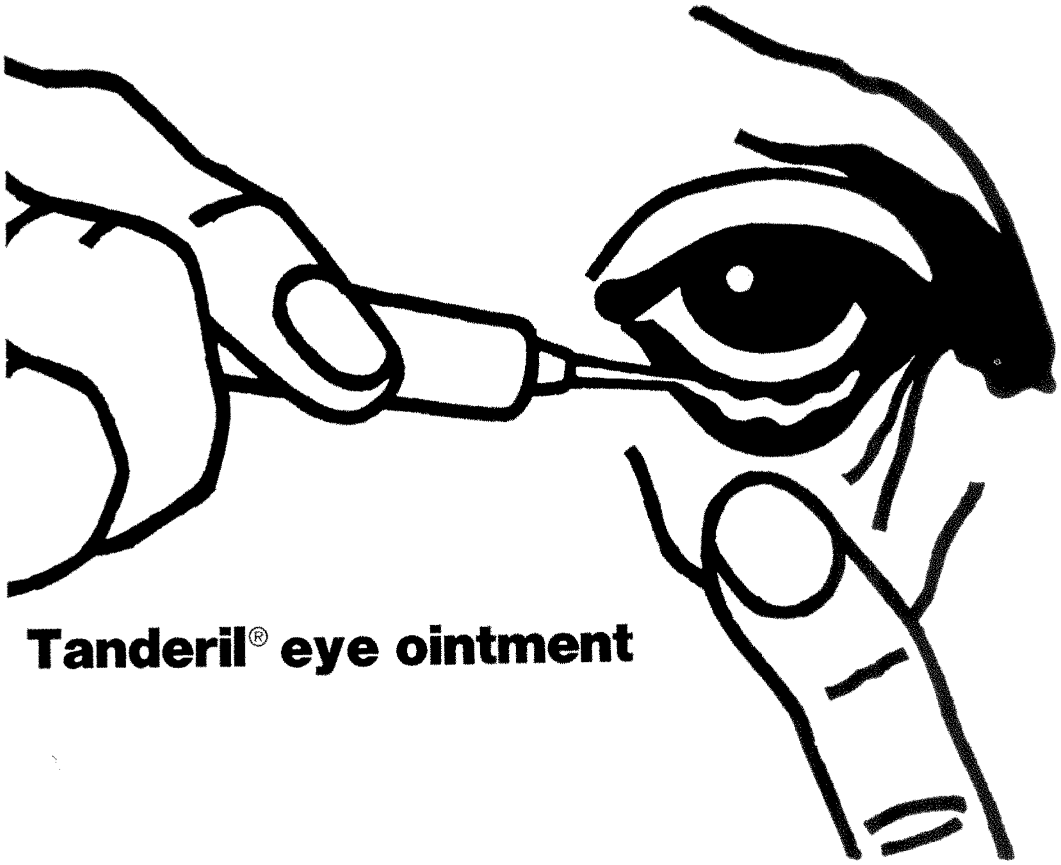

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toms, but in high dose (1500 rads) vision was reduced below 6/60 permanently in most patients. The reduction in visual acuity correlated in time and severity with corneal changes, which are described later.

Pain

Thirty-two patients complained of discomfort in the eyelids beginning after 20–34 days, and later in patients with conjunctival keratinization. Thirty patients complained of pain or discomfort in the eye, as early as 27 days in one patient and as late as five months in another. The average time of onset was at 10 weeks. Severe and persistent pain occurred in most patients receiving more than 1000 rads. Discomfort in the eye correlated with epithelial keratitis recorded as ++ or greater, and pain with corneal erosion in three eyes and corneal ulceration in four.

Epiphora

Epiphora occurred in 31 eyes after 8 to 19 weeks. In three eyes it was present initially and was aggravated after neutron therapy. Epiphora was transient in low-dose patients, remitting at about 12 weeks and persisting in only 13 eyes. The causes of epiphora are considered later.

CLINICAL EFFECTS—SIGNS

Skin erythema (Table II, Fig. 1)

Erythema of the face and eyelids occurred in 52 patients seen during the early weeks of treatment. Four patients were not examined during the appropriate period. The reaction was seen as early as 15 days, reaching a peak at 25 days, and thereafter subsiding to disappear at 10–12 weeks. In no case did erythema persist, but it was followed later in some patients by telangiectasia and in two by increased skin pigmentation.

Table II *Percentage incidence and nature of signs occurring in the face, eyelids, and lacrimal system related to radiation dose*

Sign	*Radiation dose (rads)* ⩽100 ($n=28$)	101–300 ($n=28$)	301–500 ($n=13$)	501–1000 ($n=8$)	>1000 ($n=16$)
Erythema of face	32	54	77	100	69
Erythema of lids	7	54	77	88	56
Oedema of lids	10	25	77	73	75
Mucopurulent discharge	4*	25	54	75	63
Loss of cilia	10	29	85	50	81
Meibomian obstruction	10	32	69	50	88
Punctal stenosis	10	18	31	38	69
Distortion of lid contour	7	36	38	50	75
Punctal ectropion	10	25	23	38	50
Tear fluid excess	18	46	46	50	69
Tear fluid deficiency	7	18	15	13*	44
Precorneal drying	4*	11	23	50	31
Oil excess	14	36	38	25	31
Oil deficiency	—	18	46	25	56
Mucus excess	18	36	62	63	88
Debris excess	21	39	69	63	88

*Only one eye affected

Eyelids (Table II, Fig. 1)

Oedema. This was seen in 37 eyes and coincided with the appearance and subsidence of the erythematous response, but when an eyelid received a dose of over 1000 rads it persisted and in some cases increased.

Loss of cilia. Partial or complete loss of cilia was

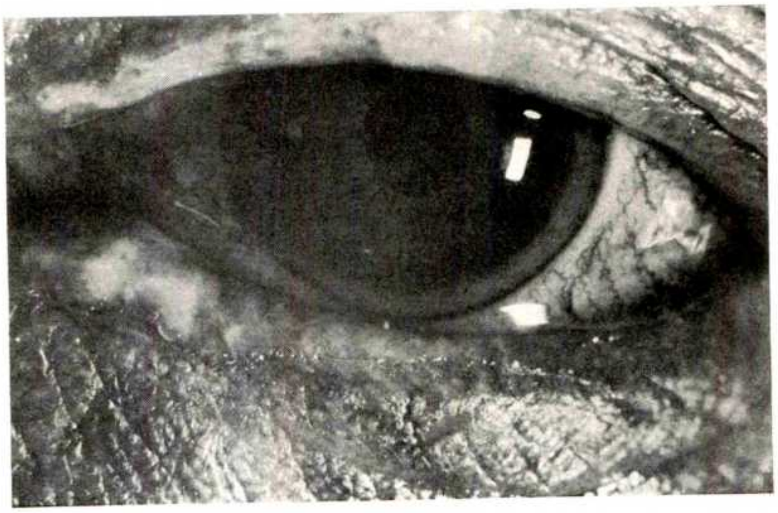

FIG. 1 *Eye at 35 days showing skin and conjunctival erythema, skin oedema, loss of cilia, distortion of lid margin contour, mucopurulent discharge, and excessive tear fluid in marginal gutter*

common. Reduction in the number of lashes occurred between 22 days and eight weeks with complete loss by 30 days to 19 weeks. In only two patients was there any regrowth.

Distortion of lid contour. Rounding of the posterior edge resulting in imperfect lid apposition to the globe occurred in 33 eyes. This distortion appeared between 18 and 49 days, tended to persist, and disappeared in only one patient. The amount of distortion paralleled that of the oedema and increased later (19 weeks to five months) in patients in whom the oedema increased.

Meibomian gland obstruction. Obliteration of meibomian orifices occurred in 39 eyes. It was first seen after 15 to 34 days and tended partially to remit later. It was associated with absence of the oily layer of the tear film. In late cases (after four months) accumulation of secretion was seen through the conjunctiva in some tarsal glands which had not reopened.

Mucopurulent discharge. This commonly collected along the lower lid margin and at the inner canthus in spite of the routine use of antibiotic drops. It was thought to be due to abnormal tear film constituents rather than infection. All cultures were sterile and microscopy showed that the constituent cells were leucocytes.

Lacrimal function (Table II)

Lacrimal punctal stenosis. Partial punctal obstruction developed in 27 eyes after 17 to 34 days and progressed to become complete in 11 cases. In the less affected cases partial remission occurred by 5 months.

Lacrimal punctal ectropion. Ectropion occurred in 24 eyes after 18 days to 12 weeks. The condition tended to remit when lid oedema subsided but persisted to some extent in most cases.

Naso-lacrimal duct obstruction. This occurred bilaterally in two patients at 19 months, probably as a result of radiation. Uncomplicated bilateral dacryocystorhinostomies were performed with relief of symptoms in one patient.

Tear fluid. This was seen in excess in 39 eyes after 15 days to 12 weeks and tended to persist (Fig. 1). Seventeen eyes developed a deficiency with onset of corneal drying between 38 days and 13 weeks, which tended to persist.

Tear film constituents. There was excessive oil in the tears in 25 eyes between six days and 15 weeks with return to normal in 11 to 19 weeks or progression to deficiency in 22 eyes. Mucus was excessive in 42 eyes after 18 days to 15 weeks and persisted. Excess debris of a fine, white cellular appearance was observed in the tear film in 46 eyes after 14 to 38 days with subsequent disappearance at 20 weeks. Microscopy showed it to consist of leucocytes and in one case also erythrocytes.

Conjunctiva (Table III)

Conjunctival injection (Fig. 1). Injection was observed in 40 eyes. There was dilatation of the arterioles, capillaries, and venules, particularly in the tarsal conjunctiva. The global conjunctiva was less affected. Injection was first observed at 13 days, reached a peak at 27 days, and thereafter subsided slowly. The course paralleled that of the skin erythema but the decline seemed to take longer and result in a pathologically pale appearance. The pallor was due to a relative absence of blood-filled capillaries; the arterioles appeared relatively normal at this stage.

Telangiectasis (Fig. 2). Telangiectasis was seen in 26 eyes on average at 25 weeks, and in all cases had been preceded by a significant degree of erythema (++ to ++++). Differentiation between injection and telangiectasis was not always easy. Telangiectasis was recognized as dilated arterioles, straight in the tarsal conjunctiva and tortuous on the bulbar conjunctiva, from which normal or enlarged capillaries branched at right-angles.

Oedema. Chemosis was seen in 17 eyes from 18 days onwards and occurred only in association with moderate or severe (++ to ++++) erythema. The oedema subsided by 43 days, except in one severe case in which it persisted.

Table III *Percentage incidence and nature of signs occurring in the conjunctiva and cornea related to radiation dose*

Sign	*Radiation dose (rads)* ≤100 ($n=28$)	101–300 ($n=28$)	301–500 ($n=13$)	501–1000 ($n=8$)	>1000 ($n=16$)
Conjunctival injection	4*	50	77	75	69
Conjunctival oedema	4*	14	46	38	50
Conjunctival ulcer	—	—	—	—	13
Telangiectasia	10	25	8*	50	50
Keratin formation	4*	7	8*	25	38
Contracture	4*	4*	15	—	13
Corneal erosion	—	—	23	13*	31
Epithelial keratitis	7	36	46	38	63
Reduction of corneal sensation	4*	18	15	25	50

*Only one eye affected

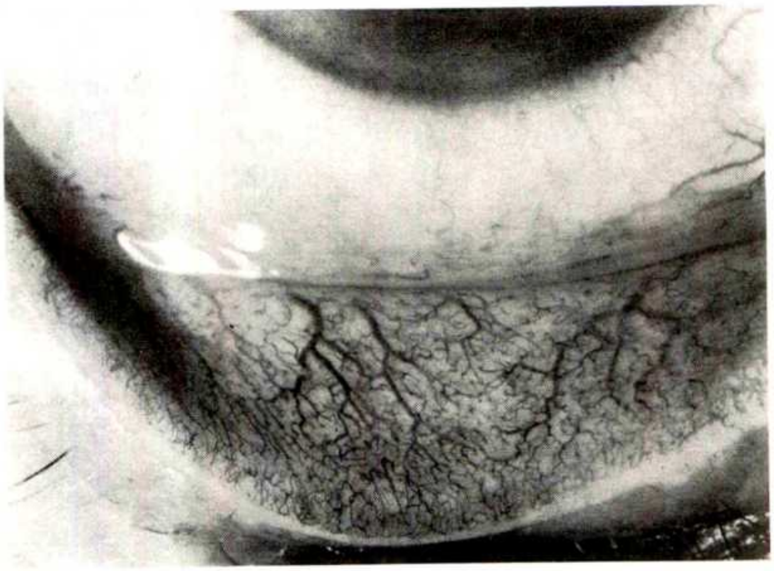

FIG. 2 *Telangiectasia of tarsal conjunctiva*

Ulceration. This was seen in only two patients in association with other notable signs of radiation. The conjunctiva of the lower fornix was affected in both and the global conjunctiva also in one patient. It occurred relatively late, after 11 weeks.

Contracture. Contracture of the conjunctiva was a relatively late sequel in six eyes after 13 weeks.

Keratinization (Fig. 3). Keratin plaques appeared after 10 weeks in 12 eyes on the tarsal conjunctiva near the lid margins and occasionally encroached on the global conjunctiva. They tended to vary in size and position from one examination to the next. In three eyes they disappeared and were replaced by normal epithelium.

Cornea (Table III)

Epithelial keratitis. Punctate epithelial keratitis of minor degree was a common finding and caused slight loss of visual acuity and discomfort. It occurred in 32 eyes after 15 days, reached a peak at 30 days, and thereafter declined slowly with complete healing after 10 weeks in most eyes but with some degree of persistence in others.

Corneal erosion (Fig. 4). Epithelial keratitis was

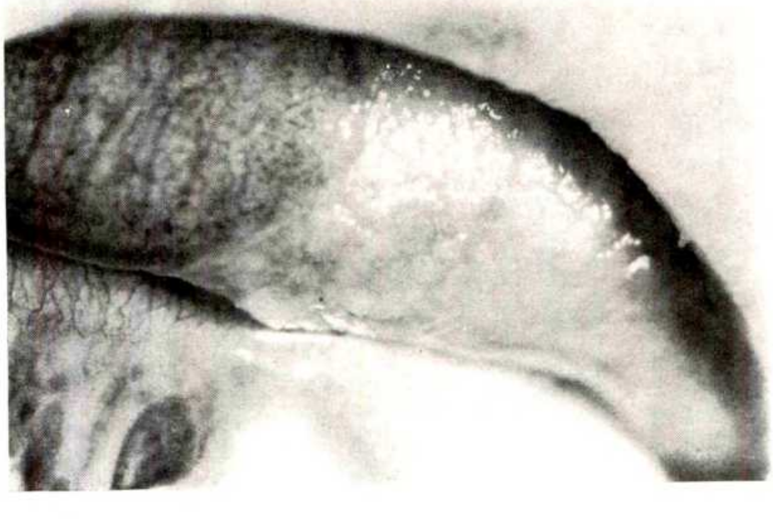

FIG. 3 *Keratin plaque on upper tarsal conjunctiva*

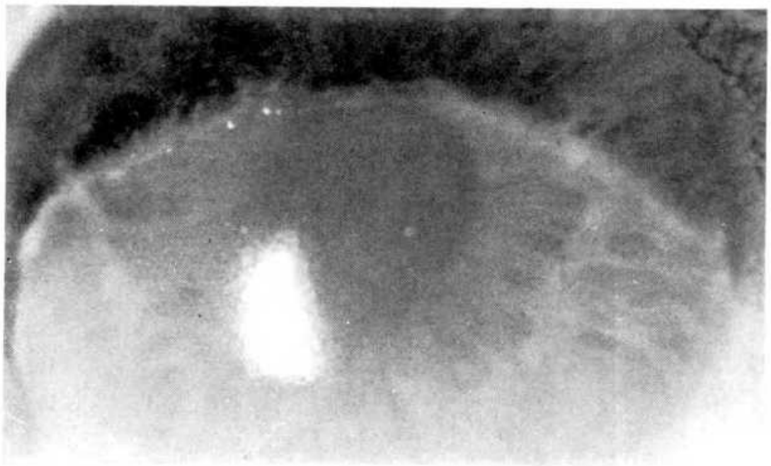

FIG. 4 *Extensive corneal erosion*

followed in 11 eyes by corneal erosion. In four eyes the erosion increased over four weeks to produce total corneal epithelial loss. Epithelial regrowth occurred in some eyes and was sometimes accompanied by wedge-shaped patches of conjunctival epithelium (Fig. 5) which later came to resemble corneal epithelium.

Corneal ulceration. This occurred as a late complication (after two to nine months) in four eyes. In one eye it responded to medical treatment, but in another it perforated and the eye was lost. One eye was successfully treated by a corneal graft. The fourth patient died before observations could be completed.

Corneal sensitivity. This was reduced in 19 eyes, including those with total corneal erosions.

Uvea (Table IV)

Iris atrophy was a late sequel in three eyes after eight weeks. There was partial loss of the pigment epithelium, visible on transillumination. Rubeosis iridis occurred in one eye (see 'Intraocular pressure').

Lens (Table IV)

Radiation cataracts developed in 11 eyes and presented between 34 weeks and 19 months, most commonly between seven and 12 months. All those presenting after one year had not been examined between 12 months and the time of presentation. The earliest changes were often identified from the slit-image photographs. The cataracts consisted of fine granular and cystic material in the posterior subcapsular region of the lens (Fig. 6). In the less affected eyes the changes

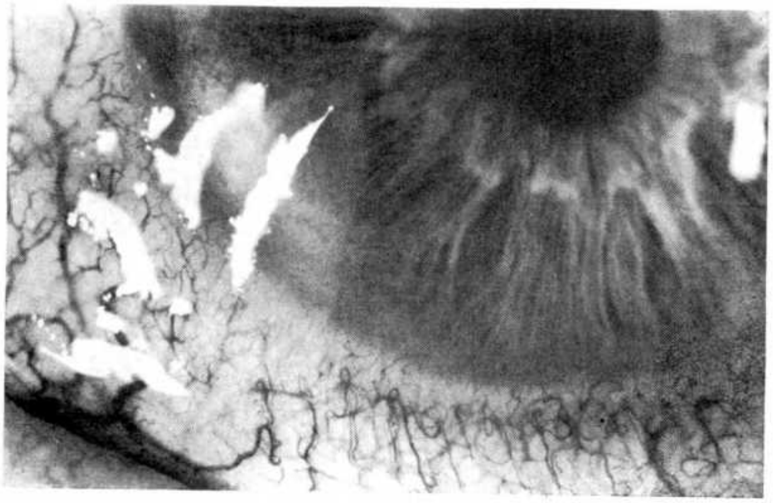

FIG. 5 *Wedge-shaped patch of conjunctival epithelium is seen on cornea after healing of corneal erosion. Telangiectasia of bulbar conjunctiva*

Table IV *Percentage incidence and nature of signs occurring in the uveal tract, lens, and retina related to radiation dose*

Sign	*Radiation dose (rads)* < 100 ($n = 28$)	101–300 ($n = 28$)	301–500 ($n = 13$)	501–1000 ($n = 8$)	> 1000 ($n = 16$)
Iris atrophy	—	4*	—	—	13
Radiation cataract	4*	4*	31	—	44
Retinal pigment	—	—	8*	—	13
Glaucoma	—	4*	—	—	—

*Only one eye affected

were confined to the posterior pole, but in the three more severely affected there was thinning of the anterior subcapsular clear zone with some fine granular deposits arranged in radial lines in the equatorial periphery of this zone. In three eyes the posterior subcapsular opacities increased in density to the point where cataract extraction was indicated. Cataract extractions were uncomplicated in these cases. In three eyes mature cataracts developed rapidly in association with penetrating corneal ulcers. This occurred at seven months in one eye and at 15 months in the other.

Retina (Table IV)

Pigmentary retinopathy with a few microaneurysms was observed in three eyes at seven months. There was a fine scattering of pigment around the posterior pole, but normal electro-oculograms showed that there was no widespread disturbance of the retinal pigment epithelium. Central retinal artery occlusion occurred in one eye at 30 months. This eye had received 1252 rads.

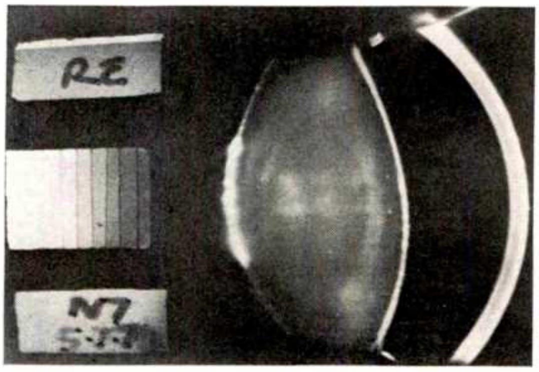

FIG. 6 *Slit-image picture of lens showing developing posterior subcapsular cataract, absent anterior subcapsular clear zone, and fine anterior subcapsular cataract forming*

Intraocular pressure (Table IV)

Reduction in intraocular pressure occurred in nine eyes after 29 days. Two recovered normal levels after 11 weeks, but the other seven remained low. In one patient the final figure was significantly low at 6 mmHg. One eye developed absolute glaucoma in association with rubeosis iridis.

Loss of vision or loss of eye

Five eyes either lost all useful vision or became damaged beyond hope of recovery. With the exception of the glaucomatous eye (325 rads) and the eye with central retinal artery occlusion (1252 rads), loss of sight occurred only at doses greater than 1500 rads. In these eyes the sight was lost as a result of corneal ulceration and perforation due to corneal necrosis, and self-induced mechanical damage may have contributed in one of these cases in which the cornea was anaesthetic.

Discussion

Several papers, mainly American in the 1950s, have reported the effects of neutron irradiation resulting from cyclotron accidents (Ham, 1953; Haye, Mathé, Jammet and Pendic, 1970); from chronic exposure in cyclotron workers (Ableson and Kruger, 1949; Dollfus, 1950); and from atom bomb explosion (Flick, 1948; Cogan, Martin, and Kimura, 1949; Cogan, Martin, and Ikui, 1950; Kimura and Ikui, 1951; Ham, 1953).

We know of none on the effects on the human eye of deliberate clinical exposure. Deliberate exposure has been confined to animal experimentation (Krause and Bond, 1951; Cogan, Goff, and Graves, 1952; Moses, Linn, and Allen, 1953; Haye, Legeay, Bazin, and Quechon, 1970).

The relevance of the literature to the present study is not easy to assess. The type of radiation is not identical and the significance of the dose is uncertain. In accidental exposures the doses are necessarily vague and in animal experiments, where the doses are monitored, the relevance of the findings in an infant animal to the treatment of adult humans is questionable. Nevertheless, the literature is useful in describing the clinical features to be expected, particularly those of cataract. The histology of neutron cataract is described and the mechanism of its formation suggested. The animal experiments, in particular those of Krause and Bond (1951) and Cogan and others (1952), suggest that neutrons are more cataractogenic per unit energy than x rays, and we expected that cataract would be the chief complication of neutron therapy. This proved not to be the case.

Kimura and Ikui (1951) and Cogan and Donaldson (1952) described doughnut-shaped posterior cortical cataracts in patients exposed to atom bomb irradiation. Histological examination showed granular material at the posterior pole and abnormal equatorial cells. In our study single-layered opacities occurred in the posterior subcapsular region and doughnut shapes were not seen. There were changes in the anterior subcapsular region, with obliteration of the subcapsular clear zone, followed by subcapsular cataract. This has been seen in cataracts from other causes (Brown and Tripathi, 1974). The opacities consist initially of a fine granular and cystic material in the lens periphery which is seen to move towards the poles, especially the posterior pole, on sequential observations. These observations support the view that it is the lens epithelium that is most sensitive to neutron irradiation, as suggested by Kimura and Ikui (1951), and to *x* irradiation, as suggested by Grzedzielski (1935), Okusawa (1933), and Leinfelder and Kerr (1936).

OTHER OCULAR EFFECTS

The literature on neutron radiation is concerned mainly with cataract. In our study we found significant changes in eyelids, conjunctiva, and cornea. Such changes also occur in *x* irradiation (Duke-Elder, 1954; MacFaul and Bedford, 1970; Merriam, Szechter, and Focht, 1972). We considered the temporary dysfunction in the eyelids of our patients to be due to vessel damage, with resultant erythema and oedema, and to damage to epithelial structures, causing epilation and meibomian gland obliteration. This was followed either by resolution with clinical recovery or fibrosis with resultant permanent dysfunction, including meibomian obliteration, ectropion, lacrimal punctal stenosis, and persistent oedema.

The lacrimal apparatus was affected by both epiphora and dry eyes. Epiphora was accounted for by punctal stenosis, naso-lacrimal duct obstruction, and reflex increase in tear production in response to corneal irritation. Keratoconjunctivitis sicca, which occurred in the more severely irradiated eyes, may be due to reduced tear secretion either as a result of destruction of the ductules of the lacrimal glands passing through cicatrization in the conjunctiva or as a result of destruction of the gland itself or of the accessory glands.

Abnormalities in the quality of the tears were also found. They were less able to wet the cornea on blinking and the precorneal tear film tended to dry between blinks—which was attributable in part to meibomian gland destruction with the resultant loss of the oily layer of the tear film. The particulate matter in the tear film consisted of leucocytes and erythrocytes which had probably entered the tears by diapedesis through the damaged vessel walls. We attributed the excess mucus sometimes seen soon after treatment to irritation of the goblet cells of the conjunctiva, and it may have been due to a goblet cell hyperplasia.

The conjunctival erythema and chemosis either resolved or went on to telangiectasia and persistent oedema. The oedema was probably due initially to an increased production of extracellular fluid from the dilated capillaries and later, when the vascularity had diminished, to reduced clearance of extracellular fluid by defective lymphatics. In severe cases there was epithelial loss, which was followed by conjunctival contracture with scarring and by invasion of the conjunctiva by squamous keratinizing epithelium from the lids.

CORNEA

The corneal epithelium was partially or, rarely, completely destroyed. This was probably due initially to radiation and the alteration in corneal environment caused by lid ectropion with exposure, and then keratin plaques and abnormalities of the tear film contributed to its persistence. The similar effects of *x* irradiation directly upon the epithelium and through diminished tear secretion have been described by MacFaul and Bedford (1970), and Maumenee (1956) described the abrasive effect on the cornea of keratin plaques on the tarsal conjunctiva.

Corneal sensitivity was affected at the time of epithelial loss, after which sensitivity usually returned. In this respect neutron radiation appears to be less damaging than *x* irradiation, which commonly significantly affects corneal sensation (MacFaul and Bedford, 1970). The corneal stroma seems relatively resistant to neutrons but we attributed the severe late ulceration in three eyes to corneal necrosis. This is a well recognized late complication of *x* irradiation (Blodi, 1958; Linnell and Wolter, 1967; MacFaul and Bedford, 1970; Merriam and others, 1972) and after radium application (Martin, 1936). We did not see stromal vascularization, which may follow *x* irradiation (Blodi, 1958). The corneal endothelium seemed resistant to the dose of neutrons used and stromal oedema was seen only at the time of epithelial loss. Once corneal epithelial healing had occurred good vision returned and persistent oedema, which may follow *x* irradiation (Blodi, 1958), did not occur.

UVEA

The uvea seems relatively resistant to neutron irradiation. Iris atrophy, a recognized effect of *x* irradiation (Benedict, Christenberry, and Upton, 1955), occurred but did not cause dysfunction.

The intraocular pressure tended to fall, suggesting dysfunction of the ciliary body and permanent damage to it in patients in whom pressure remained low. There was no disability attributable to the low pressure. Rubeosis iridis associated with glaucoma is a recognized complication of *x* irradiation (Jones, 1958; Bedford, 1966) and was seen in one neutron-irradiated eye.

RETINA

The retina seems resistant to neutron therapy. The changes in visual acuity could be accounted for by changes in the anterior segment. The minor pigmentary disturbance seen in three eyes was not associated with electroretinographic change, which is recognized in *x* irradiation (Baily and Noell, 1958; Noell, 1962; Lipetz, 1962). Radiation retinopathy with haemorrhages and exudates is known to result from cobalt plaque application to the eye (Cibis and Brown, 1955; MacFaul and Bedford, 1970; Hayreh, 1970) and is reported after intensive *x* irradiation in man (Chee, 1968; Billson, Yeung, and Crock, 1969; MacFaul and Bedford, 1970) and in experimental animals (Cibis, Noell, and Eichel, 1955). In the present study only two eyes showed small numbers of microaneurysm.

DOSE RESPONSE RELATIONSHIP TO CLINICAL EFFECT

Tables I–IV show the incidence of symptoms and signs related to neutron dosage. In another communication (Brown and others, 1976) we related dosage to clinical effect in a smaller number of eyes. We found no significant differences in the 93 eyes reported here. Our results, as reported earlier, indicate that doses up to about 80 rads produce no recognizable effect. Doses of 85 to 220 rads produce slight transient disturbance of vision and irritation followed by complete resolution. Doses of 220 to 860 rads produce a moderate disturbance of vision and discomfort with incomplete resolution resulting in a slight, permanent reduction in vision. Doses of 860 to 1510 rads commonly produce a severe clinical effect with significant reduction in vision and little resolution. Most of the patients in this group have persistently poor vision, but in some this is remedied by cataract extraction. A few patients even in the upper range of this group are symptom-free after 18 months. Doses in excess of 1510 cause ocular destruction and no useful vision is retained.

ANALYSIS OF ERRORS

There were only a few eyes in each dosage group, which makes it difficult to draw conclusions from the percentage incidence of signs and symptoms. The tendency was for the incidence of a symptom or sign to increase with dosage, with the following exceptions. In the group of patients where the dose was more than 1000 rads the incidence of facial and lid erythema, mucopurulent discharge, and conjunctival injection seemed to be low. These are early signs and not all the patients in that group were seen at the earliest stages.

The group 501–1000 rads consisted of eight patients and it was unfortunate that this group comprised some of the most sparsely documented patients by reason of irregular attendances, etc. Thus any apparent anomaly in this group must be attributed to these factors. In the group $\leqslant 100$ rads only one eye had chemosis, injection, and mucopurulent discharge. These signs were due to incidental conjunctivitis and not to radiation. In one eye with reduced corneal sensation in this group the loss of sensation was minimal.

There are some doubts about the accuracy of the dosages of radiation stated in this study, for the following reasons:

1. The lower the estimated dose the higher the possible error. Thus a stated dose of 50 rads may be ±10 rads in error, but, for example, a dose of 680 rads may be ±30 rads, a lower percentage error.
2. An eye placed at the edge of the field will receive a variation of dose across the eye. When measuring doses across the eye by aluminium activation, pellets of aluminium may also be on the edge of the field. An incorrect estimate of dose may be obtained if only part of the pellet is irradiated. In cases where this was thought to have occurred the maximum possible dose was estimated.
3. The error in calculating the doses received was of the order of 5 per cent.

ERRORS IN INCIDENCE OF SIGNS AND SYMPTOMS

The timing of follow-up varied between patients. Some were not examined until after the start of radiotherapy and there were occasional lapses in regular follow-up owing to patients not being able to attend. Thus some early signs might have been missed. Some patients were not followed-up for more than a few weeks for various reasons, and so the incidence of late complications may well be higher than that given.

Summary

This study of 93 eyes receiving neutron irradiation establishes the character of the ophthalmic complications of neutron treatment. Significant changes are produced in the eyelids, conjunctiva, and

cornea, but the production of cataract is relatively unimportant. No reaction was seen after neutron treatment that had not already been seen after *x* or gamma radiation. That the unavoidable damage is similar to that reported with other forms of radiation, and not worse, is an important finding in view of the statistically significant benefit of neutron treatment to patients in a controlled clinical trial of advanced tumours of the head and neck (Catterall and others, 1975). The observations indicate that the improved cure rates with neutrons are not obtained at the expense of inflicting greater damage to normal structures. This investigation has also shown that the neutron effects of treating these very extensive tumours are acceptable and that, with carefully measured doses, they are predictable.

The dose-response relationship in categories of clinical effect for a smaller series of patients, reported in Table I of our preliminary communication (Brown and others, 1976), is confirmed.

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Severe endemic trachoma in Tunisia

CHANDLER R. DAWSON,* TOUFIQUE DAGHFOUS,† MOHAMMED MESSADI,† ISAO HOSHIWARA,‡ AND JULIUS SCHACHTER§
From the Francis I. Proctor Foundation for Research in Ophthalmology and Department of Ophthalmology, University of California, San Francisco, L'Institut d'Ophtalmologie de Tunis, Tunis,† the Division of Indian Health, United States Public Health Service, Phoenix, Arizona,‡ and the George W. Hooper Foundation, University of California, San Francisco§*

Since trachoma responds to some antibiotics and sulphonamides that have been available for a generation, it has been assumed that it would by now have undergone the same precipitous decline in prevalence as syphilis and tuberculosis. The areas in which this happy expectation has been borne out, however, are only those that have enjoyed economic development (Assaad, Maxwell-Lyons, and Sundaresan, 1969; Blagojevic, Savic, and Litricin, 1973). For example, we found only 30 cases of active disease among 2800 schoolchildren recently surveyed for trachoma in Tunis. In contrast, the examination of children of the same age in a southern Tunisian oasis uncovered active trachoma in 85 per cent (Dawson, Daghfous, Messadi, Hoshiwara, Vastine, Yoneda, and Schachter, 1974).

This continuing high prevalence in economically undeveloped areas poses an especially grave public health problem which is disguised by the simple statement of overall prevalence rates. Because of widespread general improvement in public health programmes there has been an enormous increase in the number of people aged under 15 years, and it is this age group, burgeoning in rural areas affected by trachoma, that harbours the seeds of a future dramatic increase in blindness. This is preventable blindness, however, since active infectious trachoma responds to sulphonamides, the tetracyclines, and erythromycin. For this cogent reason the disease should now be vigorously attacked in undeveloped rural areas, where it continues to be both endemic and severe.

The study reported here was undertaken to quantify the prevalence of trachoma and its sight-threatening sequelae in two rural populations—one just beginning to develop economically, the other still with a traditional rural economy. The pattern of trachoma and its visually disabling lesions in these communities is probably characteristic of its pattern in endemic areas the world over. Information on the intensity and disabling complications of the disease in such communities is essential if the success of treatment is to be judged with any accuracy and if programmes are to be developed that yield the best results within the limitations of the available economic and human resources.

Population and methods

Two oasis villages in southern Tunisia were selected. One of them (Chott Sidi Abdel Sellem) was near a large town in which the pace of economic development had been accelerating for the five years before this study was undertaken. The second village (El Golaâ) was a pre-Saharan oasis whose economy was based on traditional agriculture—the cultivation of dates and vegetables on irrigated land. The climatic and certain demographic features of the two villages are summarized in Table I. Many of the men from both villages worked in other parts of Tunisia or in Europe and usually remitted part of their earnings to their families. Most of the houses were constructed of earth and

Table I *Climate, population, and income in two Tunisian villages, Chott and El Golaâ*

	Chott	*El Golaâ*
Temperature		
January		
Maximum	24 C (75 F)	24 C (75 F)
Minimum	12 C (54 F)	−3 C (27 F)
July		
Maximum	41 C (105 F)	44 C (111 F)
Minimum	24 C (75 F)	21 C (70 F)
Rainfall		
December 1970	77 mm (3 in)	32·5 mm (1·3 in)
Population		
Total	1962	1880
Percentage aged < 14 years	49·6 per cent	52·2 per cent
Annual income person	$120	$109

Address for reprints: Chandler R. Dawson, Francis I. Proctor Foundation, University of California San Francisco, San Francisco, California 94143, USA.

located outside the shady, cultivated part of the oasis. Artesian drinking water was obtained from public fountains, often some distance from the houses. Aboveground latrines were located near most houses and in the fields.

In both villages the relatively high mortality rate from infectious diseases in infancy and childhood had been dropping steadily, and children under 15 years of age constituted about one-half of the resident population. In each village there was a 'dispensaire' who distributed medications for common conditions. The consumption of tetracyclines (usually for gastroenteritis) and penicillin (usually for fevers and respiratory diseases) is shown in Table II. A physician visited Chott twice a week and El Golaâ once a week. Chott was near a town (Gabès) with a well-equipped regional hospital and readily accessible facilities, whereas El Golaâ was 28 km from a small satellite hospital with one physician and small staff who cared for a population of some 36 000.

Among young children in both villages (as in other communities in the region) an acute mucopurulent conjunctivitis began each year in May, reached an epidemic peak in October, and subsided with the onset of cooler weather (Huet, 1958; Vastine, Dawson, Daghfous, Messadi, Hoshiwara, Yoneda, and Nataf, 1974a). During the epidemic flies (for the most part *Musca* sp) were numerous. They clustered on the children's eyes and particularly on those with purulent conjunctivitis. This pattern of seasonal epidemics of purulent conjunctivitis has been well described in trachomatous areas of North Africa and the Middle East (Huet, 1958; Maxwell-Lyons and Amies, 1949).

A complete census of each village was made by a public health nurse familiar with trachoma control programmes and himself an inhabitant of the region. In addition to a record of the age, sex, family interrelationships, and primary occupation of each member of the family the census included information on each house about the type of construction, the water supply, the number of rooms, and the method of disposing of excreta.

CLINICAL EXAMINATION

We made all clinical observations with the standard biomicroscope (slit-lamp) and recorded the following signs (suggested for the 'short' examination by the Fourth Scientific Group on Trachoma (World Health Organization, 1966a)): trichiasis and/or entropion, lymphoid follicles on the upper tarsal conjunctiva, mature tarsal follicles, papillary hypertrophy on the upper tarsal plate, conjunctival scarring, superficial corneal vascularization (vascular pannus), corneal infiltration, corneal scarring, trachoma stage according to the MacCallan classification, and mucopurulent conjunctivitis.

Table II *Antibiotic consumption and medical care in Chott and El Golaâ* (1970)

	Chott	*El Golaâ*
Tetracyclines, doses* (250-mg or 100-mg tablets or 20-mg solution)	1023	404
Penicillin, doses* (1 000 000 or 500 000 units)	961	725
Medical care		
No. visits to clinics/year	1371	951
Nearest hospital (km)	2	28

*Doses per 1000 persons per annum

Since the definition and scoring of lymphoid follicles on the upper tarsal conjunctiva given by the WHO (World Health Organization, 1966a) can be interpreted in different ways by different observers we used a modified definition for this sign, which is described elsewhere (Dawson, Elashoff, Hanna, and Wood, 1968). Two other departures from established WHO practice were the tabulation of trichiasis and/or entropion as a separate sign, and the measurement of the person's visual acuity at the time of the first examination.

We recorded the clinical findings for each patient on a standard form at the time of examination and later transferred the data to Holerith-type punch cards for processing.

STRATIFICATION OF CASES BY CLINICAL INTENSITY

Since the MacCallan classification of trachoma does not adequately describe the intensity of the clinical disease a simple stratification of cases was devised. From the recorded clinical scores of lymphoid follicles (F) and papillary hypertrophy (P) on the upper tarsal conjunctiva the intensity of the conjunctival inflammatory disease was classified as severe, moderate, mild, or inactive, as follows

	Follicles	*Papillary hypertrophy*
Severe	1, 2, 3	3
Moderate	3	2
Mild	3	1
	or 2	1, 2
Insignificant or inactive	0, 1	1, 2

SCHEDULE OF EXAMINATIONS OF POPULATION SAMPLED

Starting in the autumn of 1969 and continuing through the winter and spring of 1970 one of us (MM) examined the entire population of both villages. A subsample of some 20 to 25 families was selected in each village, a total of 220 residents of Chott and 180 of El Golaâ. Only families in which there was a preschool-age child with active trachoma were selected. The sample was thus deliberately biased in favour of families with active trachoma and children. The families in these two subsamples were re-examined once or twice a year by two examiners working independently.

LABORATORY STUDIES

To detect the infective load of trachoma agent we took conjunctival scrapings from the children under 15 in the subsample at the initial and all subsequent examinations and stained them with either Giemsa or fluorescent antibody, as described elsewhere (Dawson and others, 1974). Material for bacterial culture was also taken from the eyes of this group (Vastine, Dawson, Hoshiwara, Yoneda, Daghfous, and Messadi, 1974b). In addition, some of the laboratory studies of conjunctival scrapings from children participating in treatment trials in a village two kilometres from El Golaâ are reported here (Dawson and others, 1974; Dawson, Hoshiwara, Daghfous, Messadi, Vastine, and Schachter, 1975).

Results

VISUAL DISABILITY

From our measurements of central visual acuity an unusually high rate of visual impairment was apparent in individuals over the age of 30 (up to 14 per cent in El Golaâ) (Table III). Although most of this visual loss could be attributed to corneal scarring, a few persons were blind from other causes such as untreated glaucoma. In the industrialized countries of western Europe or the United States the percentage of 'legally blind' in the total population ranges from 0·05 to 0·2 per cent (World Health Organization, 1966b).

ACTIVE AND HEALED TRACHOMA

In the classification of trachoma patients 'active' trachoma corresponds to MacCallan stages I, II, and III or with intensity gradings of severe, moderate, and mild (Dawson and others, 1974; World Health Organization, 1962). All patients with 'active' trachoma show signs of inflammation, particularly lymphoid follicles on the upper tarsal conjunctiva, and all patients with 'inactive' or 'healed' trachoma show conjunctival scarring, characteristic corneal vascularization, or both. In surveys individuals without any of these signs are classified as 'trachoma negative' or stage 0.

The prevalence of trachoma in the two Tunisian villages showed that about half of the children in Chott were infected before age 2 and that the prevalence of active disease declined steadily to age 15 (Fig. 1). While all persons over 15 years of age in Chott had had trachoma in the past, only about 80 per cent of those from 2 to 15 years had been affected, and in children under age 2 the prevalence of trachoma, both active and healed, was even lower.

Table III *Visual acuity in Chott and El Golaâ*

	Chott		*El Golaâ*	
Age	*No. tested*	*Percentage with visual loss**	*No. tested*	*Percentage with visual loss**
6–9	225	—	271	0·4
10–14	252	0·5	282	1·5
15–29	318	0·3	278	1·5
≥30	511	7·0	662	14·0

*Visual acuity 20/400 (10/200) or less

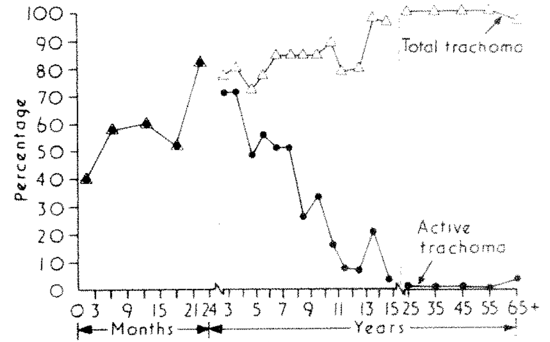

FIG. 1 *Trachoma prevalence in Chott. Active trachoma includes only inflammatory, infectious disease. Total trachoma includes all active and healed cases*

In contrast, half the children in El Golaâ had active disease by the age of 3 months and all were infected by the age of 2 years (Fig. 2). The percentage of active disease then declined up to age 15 but was still 5–10 per cent in the adult population.

INTENSITY AND PREVALENCE OF CHLAMYDIA

Severe and moderate cases of chlamydia were most prevalent in children under age 5 but had virtually disappeared by age 10 in Chott and by age 15 in El Golaâ (Figs 3 and 4). Thus the bulk of active, infectious cases occurred in the population under 15 years of age. The disproportionately large number of residents under the age of 15 was owing to recently reduced rates of infant mortality and to the emigration of adult men seeking employment elsewhere. The prevalence of trachoma agent paralleled the clinical intensity of the disease. Trachoma agent was detectable in 56 per cent of severe cases, in 20 per cent of moderate cases, and in 4 per cent of mild cases (Table IV). The

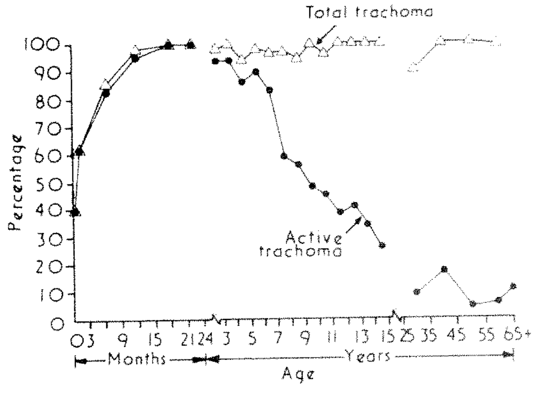

FIG. 2 *Trachoma prevalence in El Golaâ. Active and total trachoma defined as in Fig. 1*

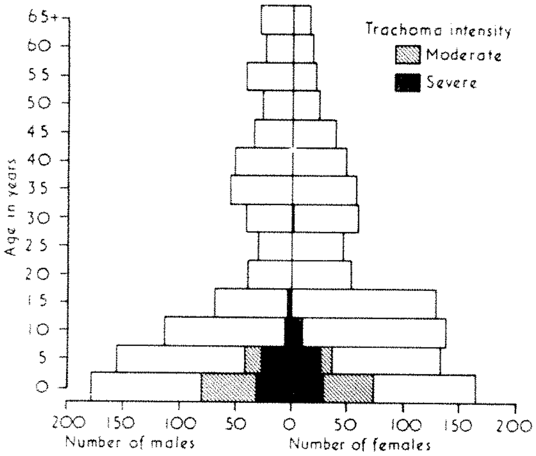

FIG. 3 *Total numbers of males and females in each 5-year age cohort in Chott and the number of severe and moderate cases of active trachoma in each cohort*

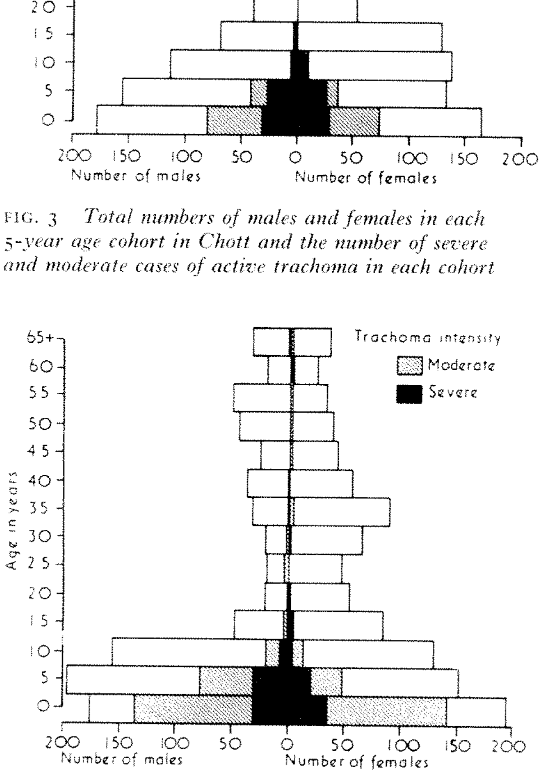

FIG. 4 *Total number of males and females in each 5-year cohort in El Galaâ and the number of severe and moderate cases of active trachoma in each cohort*

severe and moderate cases were therefore more likely to serve as sources of infection for other members of the community.

In a series of chemotherapy trials carried out in a village near El Golaâ chemotherapy only temporarily suppressed the inflammatory disease in 6- to 9-year-olds (Dawson and others, 1974; Dawson and others, 1975). In treated patients, however, there was a four to tenfold decrease in the prevalence of chlamydia-positive smears in the various intensity groups (Table IV). Thus antibiotic treatment may reduce the transmission of the agent more than would be expected from its clinical efficacy.

DISABLING LESIONS

Active trachomatous inflammation of the conjunctiva may progress to irreversible conjunctival and corneal scarring that threatens blindness and to corneal scarring that actually causes visual loss (Fig. 5). Conjunctival cicatrization first manifests itself as linear scars (Fig. 6), but in severe cases the lid margins become distorted and abrade the eyeball and cornea either with individual cilia (trichiasis) or by the whole inturned lid margin (entropion) (Fig. 7). The cornea, which in agricultural communities is already often exposed to minor trauma and foreign bodies, may thus be subjected to constant abrasion by the inturning eyelashes. Diffuse scarring of the conjunctiva also reduces the aqueous and mucous components of the tears and in this way produces a relatively 'dry eye'. Without an adequate protective tear film minor corneal abrasions may easily become infected and lead to corneal ulceration, scarring, and loss of vision (Fig. 7).

In this study trichiasis or entropion, or both, and the severest grade of conjunctival scarring were considered to be *potentially* disabling, and severe central corneal scarring (grade 3) was considered to be *actually* disabling. Severe corneal scarring rarely occurred in the absence of trichiasis/entropion or severe conjunctival scarring. The presence of potentially or actually disabling lesions increased sharply at 20 years of age in both villages (Fig. 8). In Chott there was a slight increase in potential disability at age 45 and an increase in actual disability at age 40. In El Golaâ potentially disabling lesions appeared in some 5- to 10-year-olds, increased in incidence up to age 30, and affected 35 per cent to 45 per cent of the population after age 30. Severe corneal scarring occurred early in El Golaâ, affecting a significant proportion of persons by age 25 and increasing dramatically

Table IV *Trachoma intensity and prevalence of agent before and after chemotherapy*

Intensity	*Giemsa and/or FA positive*			
	Before treatment		*After treatment*†	
	No. positive/ No. tested	*Percent positive*	*No. positive/ No. tested*	*Percent positive*
Severe	53/94	56	10/49	20*
Moderate	44/220	20	11/237	4·6*
Mild/ inactive	2/47	4	1/120	1

*Prevalence of agent and intensity of disease significantly lower in antibiotic-treated groups ($P < 0·01$)
†With topical tetracycline or rifampicin

over age 50, although the overall rate of potential and actual disability did not change (Fig. 8).

Although the incidence of disabling lesions increased to age 35 in both villages, acute inflammatory disease almost disappeared by age 15 (Figs 3 and 4). Since scarring is undoubtedly a direct result of the inflammatory process this apparent 10- to 20-year lag was probably attributable to a low but persistent rate of inflammatory disease in adult life, leading to an accumulation of disabling lesions, or to a shrinking of conjunctival scars produced in childhood, with resultant occurrences of trichiasis or entropion years after the healing of the inflammatory disease.

The accumulation of corneal scars in still older adults may reflect cumulative corneal damage from trichiasis/entropion, foreign bodies, and bacterial infections, probably worsened in advancing age by loss of tears and trachomatous scarring.

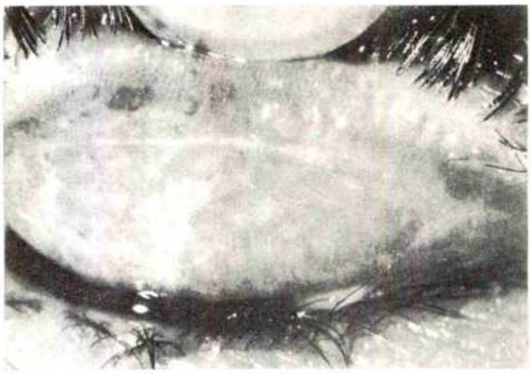

FIG. 5 *Conjunctiva of everted upper eyelid with severe intensity trachoma in 6-year-old child. One linear scar can be seen but papillary infiltration obscures blood vessels and follicles*

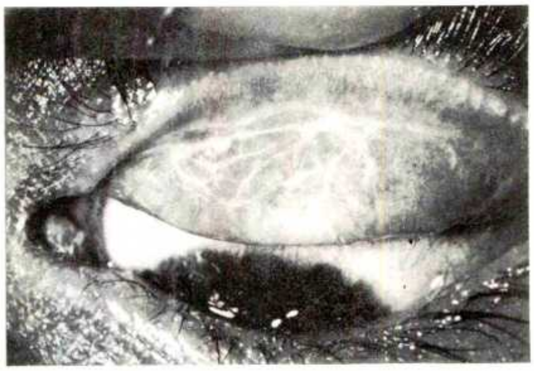

FIG. 6 *Same eye as Fig. 5 after three weeks' treatment with topical tetracycline. Inflammation has subsided revealing scarring severe enough to threaten visual acuity*

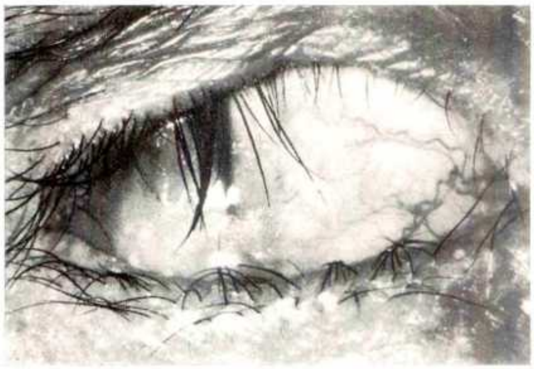

FIG. 7 *Trichiasis and resultant corneal scarring in adult with healed trachoma*

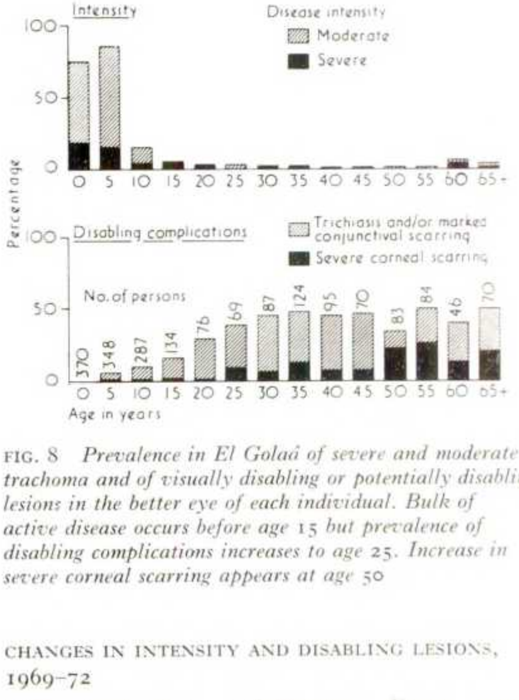

FIG. 8 *Prevalence in El Golaâ of severe and moderate trachoma and of visually disabling or potentially disabling lesions in the better eye of each individual. Bulk of active disease occurs before age 15 but prevalence of disabling complications increases to age 25. Increase in severe corneal scarring appears at age 50*

CHANGES IN INTENSITY AND DISABLING LESIONS, 1969–72

Since most of the inflammatory disease was in children under 10 years of age the distribution of trachoma intensity in this age group was evaluated in population subsamples (Fig. 9). In both villages there were initially more active cases in the subsamples than in the entire population, a result of selecting for the subsamples only families with a trachomatous preschool child. When children under 10 in these same families were re-examined in 1972 the situation in El Golaâ had remained virtually unchanged. Despite the subsample bias towards disease activity the overall intensity of the disease had decreased dramatically in Chott. During this period the construction of an electric

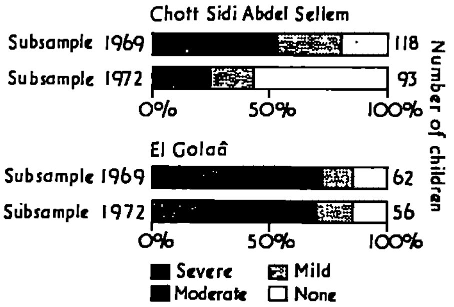

FIG. 9 *Active trachoma in a selected subsample of children under* 10 *years of age in each village in* 1969 *and* 1972

generating plant and chemical fertilizer plant immediately adjacent to Chott had led to a marked economic improvement in the village.

Conjunctival inflammation tended to mask the conjunctival scarring (Figs 5 and 6). Thus an apparent increase in scarring in Chott, or example, may have been due in part to the 'unmasking effect' of the decrease in inflammation. There was no suggestion that scarring in itself was necessary for healing.

BACTERIAL PATHOGENS

In both villages seasonal epidemics of purulent conjunctivitis started in early summer and reached a peak in late October. As reported elsewhere (Vastine and others, 1974a, 1974b), the epidemic disease, which was always more severe and widespread in El Golaâ, was associated with *Haemophilus* sp., pneumococci, *Moraxella* sp., and *Staphylococcus aureus* but not with *Streptococcus viridans* or diphtheroids. Such seasonal epidemics of purulent conjunctivitis are commonly associated with endemic trachoma, and in some regions with Neisseria infection as well (Maxwell-Lyons and Amies, 1949). In Tunisia we have found *Neisseria* sp. in only a few cases, however, despite special efforts to recover them on special bacteriological media (Vastine and others, 1974a, 1974b). From other studies we have learned that the ocular bacterial pathogens are eliminated by 10 or 12 days' antibiotic treatment, but that the 'non-pathogens' persist (Vastine and others, 1974a; Dawson and others, 1975).

LIVING STANDARDS AND INTENSITY AND GRAVITY OF TRACHOMA

It has been known that the poorer the community the more severe is the trachoma. The environmental influences that bring this about have not been clearly identified, although lack of water, which so often characterizes desert populations, is often incriminated. In the hope of identifying the most important factors we compared the intensity and complications of trachoma in El Golaâ (the most severely affected village) with crowding, type of housing, water supply, and the presence of children under 5 years of age.

In children up to age 9 and in adults over 30 there was a suggestive association (probability between 5 and 10 per cent) of trachoma and crowding (three or more persons per room). In people over 15 years of age the type of housing (single family dwelling, multiple family dwelling, or tent) was significantly associated (probability less than 5 per cent) with the presence of potentially disabling lesions. The presence of children under age 5 in the household had a suggestive association with intensity in 10- to 14-year-olds (who often tend their younger siblings) and a significant association with complications in 15- to 29-year-olds. The water supply (public fountain or spring) had a suggestive association with disease intensity only in children under age 5, but it also had a suggestive association with complications in 6- to 14-year-olds and a significant association in adults over 30.

Thus no single factor was clearly associated with disease intensity, although crowding and the water supply could have played some role. The high correlation of the disabling lesions of trachoma with poor housing and an inadequate water supply suggests that the most severely affected individuals are probably the poorest members of the community.

CONTROL MEASURES

The major efforts currently under way for the control of trachoma consist of, first, a mass antibiotic therapy programme among schoolchildren in the first and third school years. In endemic areas, like Chott and El Golaâ, two applications of chlortetracycline ointment are made daily for five consecutive days each month from January to June. Secondly, a three-day conjunctivitis control programme ('anti-Mrad') each October when an effort is made to treat all the children in the country with chlortetracycline ointment.

In a series of controlled therapeutic trials reported elsewhere (Dawson and others, 1974; Vastine and others, 1974a) treatment was given to primary schoolchildren and the clinical and microbiological findings were evaluated. When compared with treatment with boric acid ointment, topical applications of tetracycline, chlortetracycline, erythromycin, and rifampicin all resulted in a suppression of clinical intensity and detectable trachoma agent. Within four months of completing treatment, however, there were no clinical differences in antibiotic- and boric-acid-treated children. On the other hand, the prevalence of detectable trachoma agent was less than would have been expected in disease of such intensity (Table IV). Thus, while the effect of treatment on the clinical course of the individual case was apparently transitory, antibiotic therapy reduced the prevalence of demonstrable agent and thus probably the transmission of the disease in the community.

Discussion

In these studies the intensity of trachoma in any one individual tended to remain relatively stable. The degree of intensity might be expressed as a stochastic process determined not only by microbial pathogens but also by environmental and host factors (Fig. 10). The pathogens include both the chlamydia and the ocular bacterial pathogens. Although we could not identify with certainty the environmental features of importance, the presence of young children in the household, crowding, and the unavailability of water for household use appeared to play a role. The overall economic level of the community was apparently also important. The single most important host factor was age, almost all of the active disease occurring in children under the age of 10 years.

The disabling complications of trachoma are the result of scarring brought about by active inflammation. In this study it appeared that only patients with disease of severe or moderate intensity for considerable lengths of time developed the severe scarring that leads to visual loss.

In a population with severe endemic trachoma the risk of acquiring the disease and of developing its disabling complications are presented schematically in Fig. 11. In El Golaâ 75 per cent of the children developed trachoma of severe or moderate intensity between birth and 9 years of age. Of these, two-thirds (or 50 per cent of the total number of adults) developed potentially disabling lesions, and in one-half of these (or 25 per cent of the total) severe corneal scarring and visual loss supervened. The pattern of active inflammatory trachoma and visual disability in these two Tunisian villages is probably typical of other undeveloped areas where the disease is still endemic. With economic development the prevalence of active trachoma of severe and moderate intensity declines (as in Chott) and few if any cases develop potentially blinding lesions. In the absence of economic improvement, however, the children with severe or moderate disease develop sufficient scarring by age 15 to make blindness an inevitable consequence for at least some of them.

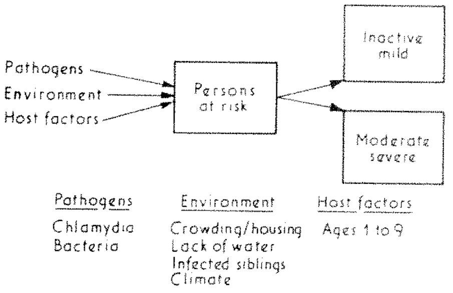

FIG. 10 *Factors influencing intensity of trachoma in childhood. Intensity in each child tends to remain stable*

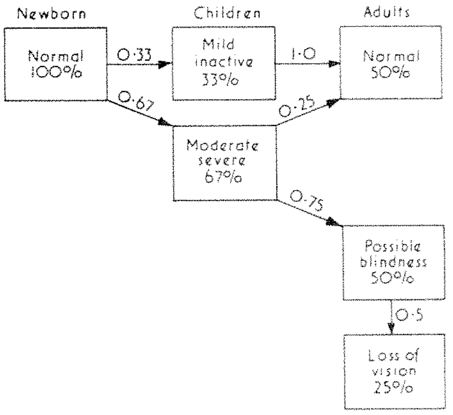

FIG. 11 *Flow diagram showing the sequence of events leading to blindness from trachoma in El Golaâ. Percentages in each box indicate proportion of children with active disease and of adults with complications. Numbers over arrows indicate probability of individuals in one category passing to next category indicated by arrow*

Since the number of children surviving to adulthood is now much greater than in the past the need for medical services for the correctable problems (for example, surgery for trichiasis) will grow correspondingly, and any success in controlling childhood trachoma *now* will ease the demand for medical care and rehabilitation of the blind only 10–20 years from now. As time goes on, the visually disabled in endemic communities will add immeasurably to the medical, economic, and social burden of affected countries, and for this reason these communities should be the focus of public health programmes for trachoma control. Since the resources for trachoma control in affected countries are limited control efforts should be concentrated in the regions where the disease is most widespread and has the highest prevalence of severe or moderate cases.

Although the present forms of local chemotherapy produce only limited clinical results they seem to have some generally beneficial effects. Systemic chemotherapy on a mass scale (as practised elsewhere) might be more effective but would carry unacceptable risks (drug reactions, increase in incidence of drug-resistant intestinal pathogens) in a population that could not be followed adequately (Hoshiwara, Ostler, Hanna, Cignetti, Coleman, and Jawetz, 1973). While newer methods of drug delivery to the eye such as the Ocusert device (Richardson, 1975) may result in a dramatic breakthrough in treating the active disease, the administrative framework of the control programme should also be improved so that preschool children could be treated and the efficacy of the control measures could be assessed regularly.

Economic development seems to offer the ultimate solution to preventing blindness from trachoma. While the many young adults who emigrate from endemic regions present little risk of infecting others in urban settings the uncontrolled inflammatory disease among children in affected villages will continue to produce scarring and eventual visual loss. Blindness from trachoma can be prevented only by controlling the disease in these severely affected rural areas. Even with the improved methods of antibiotic delivery now available much would be gained by concentrating resources on heavily affected communities and by utilizing medical assistants to the greatest possible extent.

Summary

In two villages in southern Tunisia where trachoma was endemic 7 per cent and 14 per cent of adults respectively had visual acuity of 20/400 or less. In both villages active trachoma affected most children under the age of two, reached a peak in two- to five-year-olds, then declined to age 15. The chronic inflammatory disease in childhood appeared to produce irreversible scarring of the eyelids, and loss of vision occurred in adult life due to corneal scarring caused by inturned eye lashes and loss of tears (dry-eye syndrome). Economic development in one village was associated with a decline in active, infectious disease. In the second village, whose traditional economy was unchanged, there was the same prevalence of active disease over a three-year period.

Unless economic development or public health control programmes reduce the prevalence of severe and moderate trachoma children now affected will develop the same blinding lesions as their parents. With the increasing numbers of children who survive there will probably be a dramatic increase in the numbers of the blind from trachoma in 10 to 20 years. Since active inflammatory trachoma in childhood responds to tetracyclines, erythromycin, and sulphonamides the disease should be attacked in those undeveloped rural areas where it continues to lead to blindness.

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Surgical correction of trachomatous cicatricial entropion

J. H. SANDFORD-SMITH*
From the Christian Hospital, Quetta, Pakistan

The correction of trachomatous entropion and trichiasis has been practised since antiquity, and the ophthalmic literature from its earliest days has described methods for dealing with the condition. (A helpful review of the more established surgical procedures has been given by Fox (1970).)

The simplest operation is not always the best, but in areas of hyperendemic trachoma there is great pressure on limited medical resources and it may be necessary to delegate routine entropion surgery to paramedical assistants. Also the normal anatomical planes may be hard to identify in a very scarred and contracted lid; therefore, simplicity of technique is important.

The numerous procedures for the correction of cicatricial entropion are usually based on one of three original methods:

1. A skin approach with wedge resection of the tarsal plate but preserving the conjunctiva (Streatfield, 1859).
2. A conjunctival approach with preservation of the skin (Ewing, 1903; Lagleyze, 1905).
3. The insertion of a graft in the lid margin (Van Millingen, 1887).

It was not until 1955 that Wies suggested the possibility of a 'through-and-through' lid incision involving both skin and conjunctiva (Wies, 1955), a technique that had been used since antiquity but later neglected. The operation Wies described was for 'spastic' entropion of the lower lid, but it has also been recommended, sometimes with modifications, for cicatricial entropion of either lid (Ballen, 1964; King and Wadsworth, 1970; Beyer and Carroll, 1973).

Wies's technique has several advantages in the correction of trachomatous entropion. It is easy to perform and to teach, and no tissue is excised or grafted. The anterior approach is more convenient in lid surgery and as the tarsal plate and conjunctiva (the deforming structures) are incised the deformity is corrected and the lid margin free to rotate to any required position. The operation here described is basically that of Wies with some modifications to make it more suitable for cicatricial entropion of the upper lid.

Operative technique

After infiltration with local anaesthetic and adrenaline and topical anaesthetic drops to the conjunctiva, a spatulate lid guard is positioned to protect the eye and stretch the upper lid taut. (If only the central segment of the lid margin is affected a lid clamp may be used to ensure a bloodless field but it may prevent access to the medial and lateral margins of the lid.) The skin incision is made 4 mm from the lid margin and deepened through the orbicularis muscle to the tarsal plate. With blunt dissection the marginal orbicularis fibres and roots of the eyelashes are separated from the anterior surface of the tarsal plate so that this can be incised much nearer the lid margin and, if possible, slightly obliquely. The tarsal plate should be entered on its anterior surface as near to the lid margin as possible without in any way damaging the lash roots (in practice about 2·5 mm from the lid margin), and the conjunctiva pierced about 1·5 mm from the lid margin (Fig. 1).

This is the main difference from the technique of Wies. Incising the tarsal plate nearer the lid margin produces a better eversion of the marginal fragment bearing the lashes and also less deformity or shortening of the upper lid. Keeping the skin-muscle incision far from the lid margin safeguards the lash roots and the marginal blood supply. Three to four mattress sutures are then placed through the skin of the marginal fragment just above the lash line, into the substance of the tarsal plate about 2 mm above its cut edge, and back through the skin of the marginal fragment (Fig. 2).

The sutures are tied with only moderate tension and thus not requiring any rubber pegs or other method of fixation. The eversion is ensured because the conjunctiva and tarsal plate have been incised and the lid margin is therefore able to rotate freely. Should increased eversion be required the sutures need not be tied any tighter but the mattress suture should be placed higher up in the tarsal plate, thus increasing the angle of rotation. A reverse adjustment of the mattress suture will decrease the amount of eversion. This is a useful way of straightening the irregular trichiasis, which often occurs in trachoma, because some parts of the lid may require more correction than others. A considerable immediate postoperative over-correction is best aimed for because subsequent scar contracture will cause some inversion of the lid margin. Interrupted edge-to-edge skin sutures are then placed between the mattress sutures to close the wound.

After the operation the eye is padded for one day and antibiotic ointment applied daily. The skin wound usually heals in about six days, when the skin sutures may be removed, and the tarsoconjunctival wound in

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*Present address and requests for reprints: The Guinness Eye Clinic, Kaduna, Nigeria

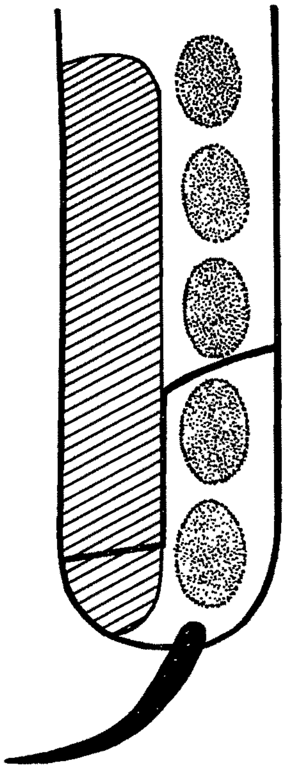

FIG. 1 *Longitudinal section of eyelid showing plane of incision*

about 12 days, when the mattress sutures may be removed. All the sutures may be removed at the later date in patients who live far away and have difficulty in making a return visit, or absorbable sutures may be used in such cases.

Results and discussion

The operation described has now been carried out several hundred times in various situations where trachoma is endemic—in a rural eye 'camp' and in a district hospital in Pakistan, and a university hospital in Nigeria. Because any systematic follow-up of the patients was impossible a report of the results is bound to be only in the form of a clinical impression.

COMPLICATIONS

Under-correction or recurrence seemed to result from several factors. First, if the conjunctival incision was not complete a small tag of uncut conjunctiva might remain and prevent easy rotation of the lid margin. Secondly, it was important to make sure that the incision extended along the whole length of the affected part of the lid or else only the central portion would be adequately corrected. Thirdly, as already noted, postoperative wound contracture meant that an immediate over-correction was desirable. With experience and an awareness of these factors the incidence of under-correction and recurrence became negligible.

Because of the severe distichiasis associated with trachoma the position of many of the lashes had often to be over-corrected in order to straighten the most inverted. So long as the over-correction involved only the lashes and lid margin and not the substance of the lid the final appearance was cosmetically acceptable. By placing the tarso-conjunctival incision as near as possible to the lid margin unsightly buckling and eversion of the substance of the lid was much less noticeable.

Granuloma formation occurred occasionally from the conjunctival wound but was easily excised with scissors without subsequent problems.

Bleeding at operation was often quite brisk from the marginal lid artery, which could be either ligated or included in one of the mattress sutures. In three cases there was quite a brisk secondary haemorrhage which was stopped by applying a firm pad and bandage.

No ischaemia of the lid margin or significant wound infection were observed, although most patients had considerable chronic conjunctivitis. Cicatricial entropion of the lower lid was less common than in the upper and usually less severe. However, it should be noted that over-correction is

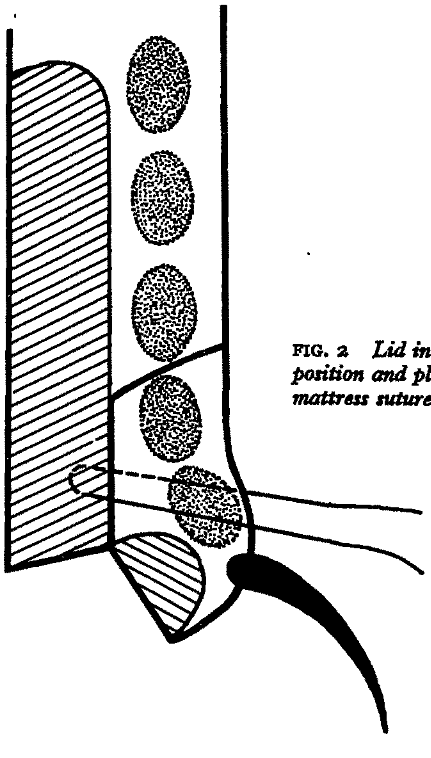

FIG. 2 *Lid in corrected position and plane of mattress sutures*

more easily produced in the lower lid, presumably because it is less rigid.

Summary

A modified version of Wies's operation for the correction of cicatricial entropion is described, the most important modification being a different plane for the incision through the eyelid. The possible complications and their prevention are discussed.

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Droplet degeneration of the cornea in North Cameroon
Prevalence and clinical appearances

JOHN ANDERSON AND HARALD FUGLSANG
Medical Research Council Grantholders, PO Box 55, Kumba,
SW Province, United Cameroon Republic

A corneal degeneration characterized by the presence of superficial hyaline deposits, which clinically resemble oil droplets, has been described under many different terms (Freedman, 1973a; Fraunfelder and Hanna, 1973). It has been reported from many areas, including Canada (Freedman, 1965; Wyatt, 1973; Young and Finlay, 1975), the USA (Fraunfelder, Hanna, and Parker, 1972; Fraunfelder and Hanna, 1973), Europe (Young and Finlay, 1975), Australia (Freedman, 1973a), South Africa (Etzine and Kaufmann, 1964; Freedman, 1973a), and SW Africa (Freedman, 1973b). Particularly severe changes have been described in Somalia (Bartolucci, 1933; Falcone, 1954; Frétillère, Védy, and Chovet, 1967), Eritrea and Saudi Arabia (Bietti, Guerra, and Ferraris de Gaspare, 1955), Red Sea islands (Zanettin, 1937; Rodger, 1973), North Africa (Gandolfi, 1962), and Iran (Barrie Jones, personal communication). Most of these studies have been of selected cases, and the prevalence of the condition in a population is unknown.

The prevalence of droplet degeneration in 517 persons aged 10 years and more among defined populations in five villages in the Sudan-savanna belt of north Cameroon is reported in this paper. The clinical appearances are described and compared with those reported elsewhere.

Materials and methods

The five villages were situated on the plain stretching eastwards from Nigeria towards Chad, on both sides of the N'gaoundéré—Garoua road, at a latitude of about 8°N. The main occupation of villagers of both sexes was subsistence farming, which involved long periods outdoors. The women were not veiled. In addition, the men engaged in hunting and fishing. The climate of north Cameroon is typical of the Sudan-savanna belt of West Africa. There is a dry season which lasts about eight months, during which the day temperature reaches very high levels, and a shorter wet season of intermittent heavy storms. Throughout much of the year the sky is clear, although in January and February there is often dust in the atmosphere blown down from the Sahara. Very high wind gusts can occur in the dry season, producing rotating columns of dust and sand.

The villages (Gorheck, Koumban, Lingerba, Naari, and Ndiki) were all included in an onchocerciasis survey in 1971–72 (Anderson, Fuglsang, Hamilton, and Marshall, 1974), during which the total populations aged five years and over were examined. The present paper is concerned with a re-examination made in January–February 1975, when all persons aged 10 years and over from the original population were studied.

Ocular examination was carried out in a darkened hut, using a Haag-Streit 900 slit lamp. Vision was tested using an illiterate E-chart, and blindness was defined as 'the inability to count fingers accurately at 3 m with the better eye'. The findings for each patient were recorded on individual record charts and sketches were made of the corneal changes.

Results

PREVALENCE

The prevalence and pattern of corneal droplet degeneration were similar in all the villages, and the results are therefore combined. Table I shows

Table I *Prevalence of droplet degeneration of the cornea, by age and sex*

	Males		*Females*		*Total*	
Age	*No. seen*	*Prevalence (per cent)*	*No. seen*	*Prevalence (per cent)*	*No. seen*	*Prevalence (per cent)*
10–19	76	0	64	0	140	0
20–29	61	3·3	84	1·2	145	2·1
30–39	46	21·7	48	12·5	94	17·0
40–49	34	44·1	33	36·4	67	40·3
> 50	46	65·2	25	52·0	71	60·6
Total	263	21·7	254	12·6	517	17·2

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Address for reprints: 54 Hornton Street, London W8 4NT

the age and sex distribution of the population examined together with the prevalence of droplet degeneration (all degrees). Corneal changes of other aetiology, mainly onchocerciasis, prevented an assessment of droplet degeneration in 23 persons, 15 males and eight females, but these cases were not excluded from the analysis. The condition was not found in those aged under 20 years, but thereafter in both sexes there was a steady increase with age. The prevalence was greater in men than women at all ages, but the difference was smaller in the older age groups. More than 50 per cent of men and women aged 50 years and over showed the condition.

CLINICAL APPEARANCES

The clinical appearances among the 89 cases were varied, but in general the changes in any individual were similar in the two eyes. It was possible to separate the changes into mild and severe.

Mild

The mildest change consisted of an exceedingly fine granularity or stippling in Bowman's zone, visible only by retroillumination. It was as if the portion of cornea was very slightly steamed up, like breath on cold glass (Fig. 1). This change was present in 78 cases (88 per cent), and was the only detectable one in 20 cases. Colourless 'droplets', of a size usually less than 0·1 mm and again only visible by retroillumination, were seen in 69 patients (78 per cent), and were the only recorded change in 11 of them. Mild granularity and droplets were present together in 58 cases (65 per cent) (Fig. 1). One or more regular, and usually circular or oval, clear spaces (lacunae) were present in the granular or stippled areas in 16 patients (Fig. 1). They seldom exceeded 1 mm in diameter and were usually considerably smaller.

These mild changes alone were present in 80 patients (90 per cent), and they were bilateral in 56 of them (70 per cent). They were confined to the peripheral 1½–2 mm of cornea in 77 cases, with the following distribution:

	Cases	*Percentage*
Temporal alone	30	39
Nasal alone	10	13
Temporal and nasal	37	48
	77	100

Thus the temporal cornea was affected in a total of 67 cases (87 per cent), and the nasal in 47 (61 per cent). In two patients mild changes were also present in the intermediate corneal zone (Fig. 4), and in one the central area was involved (Fig. 3). None of these lesions stained with fluorescein.

In about half the cases described above there was an area of clear cornea of variable extent between the lesion and the limbus. The corneal edge of these clear areas was sometimes highly contoured (Fig. 1), as described by Freedman (1965). In a few eyes the clear periphery was connected to a lacuna within the lesion, and occasionally the lesion was bisected by clear cornea (Fig. 2). In the rest the lesions seemed to extend right up to the limbus.

Central vision was reduced in 10 persons with mild lesions, but in only one of them, who showed central corneal changes, could droplet degeneration be implicated. He was a man of about 70 years, in whom bilateral cataracts were mainly responsible for the reduction of vision to counting fingers at 1 m with one eye and at 3 m with the other. The main cause of reduced vision in the other nine patients was iritis (1), cataract (5), dislocation of the lens (1), and optic atrophy (2).

Severe

Only nine patients showed changes other than granularity and formation of small droplets. They were not a uniform group, although all showed areas of granularity and/or droplets and all but one showed changes in both eyes. These are summarized in Table II, which shows that only one was a female and that most of them were aged 60 years or more. The two cases in which large protruding yellow nodules were visible were both elderly men with soft degenerating eyes. Fig. 5 represents the left cornea of the 84-year-old man, whose right cornea is shown in Fig. 4.

OTHER CONDITIONS

The prevalence of onchocerciasis in persons aged five years and over ranged from 85 to 94 per cent in the villages studied (Anderson and others, 1974). Among the 89 cases with droplet degeneration microfilariae of *Onchocerca volvulus* were seen in the cornea in 39 (44 per cent) and in the anterior chamber in 34 (38 per cent).

Pterygia were present in 16 out of the 232 villagers aged 30 years and over (7 per cent), and the prevalence was the same in cases with or without droplet degeneration.

Discussion

Most authors (Falcone, 1954; Bietti and others, 1955; Freedman, 1965; Frétillère and others, 1967; Wyatt, 1973) have emphasized the prepon-

Table II *Age, sex, visual acuity, corneal involvement, and other associated ocular lesions in nine cases with severe corneal changes*

Age	*Sex*	*Visual acuity*		*Lesion*	*Other lesions*
84	Male	R	CF3	Fine granularity and droplets almost to centre, wide clear areas nasal and inferotemporal	Cataract
		L	CF1	Central cornea totally opaque, white, with lacuna. Scattered granularity and droplets	Cataract Nasal pterygium
66	Male	R	6/6	Nasal and temporal droplets. White opacity at centre, like ground glass	Nil
		L	6/6	As R, but large lacuna within central opacity	Nil
43	Male	R	6/6	Temporal granularity and droplets. 2 isolated white ribbon-shaped opacities in band area	Nil
		L	6/6	Cornea clear	Nil
46	Male	R	6/9	Temporal granularity with lacunae. Extensive faint opacity in band area	Nil
		L	6/24	As R but with raised white plaque in nasal band	Nil
79	Female	R	PL	Nasal and temporal band opacities separated from limbus, inner borders of bands granular. Centre of cornea clear	Cataract
		L	CF1	Temporal band with related droplets, nasal granularity with droplets. Central opacity with lacuna	Cataract
36	Male	R	6/9	Faint band. Temporal cornea clear and slightly depressed, very clear inner edge bordered by white opacity. Nasal cornea similar. Scattered droplets	Flare and choroidoretinitis
		L	6/24	Nasal and temporal cornea as R. Band area clear	As R
74	Male	R	PL	Nasal and temporal plaques, ? calcified. Nasal droplets. Small central opacity	Seclusio pupillae
		L	PL	As R, but very large central opacity. Stromal vessels below	Seclusio pupillae
74	Male	R	NPL	Soft, folds in Descemet's membrane. Central mass of protruding yellow nodules with surrounding droplets	Solid flare
		L	NPL	Soft, folds in Descemet's membrane. Cornea thin, no nodules. Large white plaques nasally. Superficial nasal vessels	Solid flare
60	Male	R	NPL	Soft, folds in Descemet's membrane. White band-shaped opacity with lacunae. Large raised yellow nodule nasally	Seclusio pupillae
		L	NPL	Soft, folds in Descemet's membrane. Dense band-shaped opacity with irregular surface of white plaques. Scattered droplets. Stromal vessels below	Pseudohypopyon

derance of droplet degeneration among males, though Rodger (1973) found changes in 42 per cent of the females he examined in the Red Sea islands and Freedman (1973b) found the degeneration equally in males and females. Fraunfelder and Hanna (1973) found droplet degeneration three times more often in males than females, while Young and Finlay (1975) found changes in 64 per cent of men aged 40 and over and in only 19 per cent of women of similar age. The present study suggests that in some communities mild changes occur almost equally in males and females but that severer grades are commoner in males. It also underlines the high prevalence of droplet and associated changes in an unselected population. Its previous non-recognition throughout much of the world no doubt stems partly from its not having been sought, but partly also because the subtle changes are recognizable at examination only by retroillumination with a good quality slit lamp.

It is notable that in three separate reports of the nodular dystrophy described by Bietti (Falcone, 1954; Bietti and others, 1955; Rodger, 1973) severe cases were seen in children under 15 years of age and that the youngest case seen by Frétillère and others (1967) in Somalia was only 16. These ages are in sharp contrast to reports of corneal droplet degeneration from various parts of the world, in which the youngest ages of onset, even of mild cases, were 31 (Freedman, 1965), 46 (Fraunfelder and others, 1972), between 31 and 40 (Fraunfelder and Hanna, 1973), 35 (Freedman, 1973b), and between 30 and 39 years (Young and Finlay, 1975). In the present Cameroon study very early changes were seen in a 25-year-old man and in a 26-year-old woman. This striking difference in age incidence may suggest that the two conditions are essentially different. However,

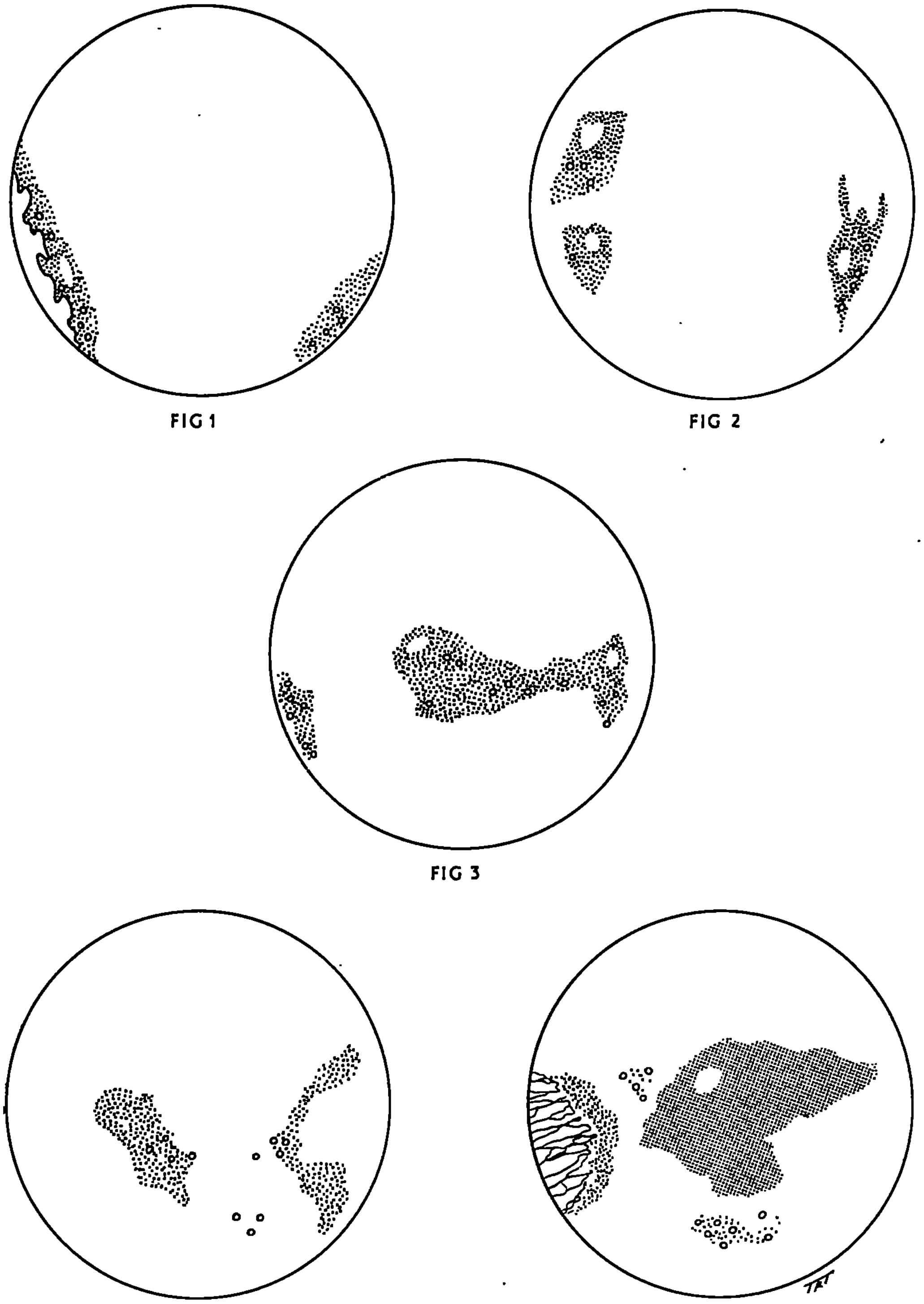

FIG 1

FIG 2

FIG 3

FIG 4

FIG 5

FIGS 1–5 *Different degrees of droplet degeneration ranging from very mild peripheral* (Figs 1 and 2) *to more severe central changes* (Fig. 5). *Areas of granularity with scattered droplets in all lesions, with dense central opacity as well as a pterygium in one* (Fig. 5) the histopathology of the lesions is the same in both (Freedman, 1973a; Garner, Morgan, and Tripathi, 1973), and possibly aetiological factors such as climate, nutritional status, occupation, and coexisting ocular disease govern the age of onset and subsequent clinical picture.

The finding of bilateral changes in 65 out of the 89 cases (73 per cent) is in agreement with most previous workers (Bietti and others, 1955; Freedman, 1965), but the secondary corneal type of Fraunfelder and Hanna (1973) was more often unilateral. In the series of 144 cases reported by Frétillère and others (1967) rather more than half were unilateral. Falcone (1954) emphasized that the lesions in Somalia nearly always appeared first on the temporal side of the cornea, and he included this as a factor in support of the aetiological role of sunlight in their development. In Labrador, however, Freedman (1965) implied that the nasal limbus was involved as often as the temporal, and his findings were supported by those of Fraunfelder and others (1972), Freedman (1973b), and Young and Finlay (1975). The present study also supports the findings of these last workers.

Droplet, or spheroidal, keratopathy or degeneration has been differently graded and classified by different workers. Freedman (1965, 1973a) distinguished peripheral from central involvement, and further subdivided the latter according to visual standard. Fraunfelder and others (1972) and Fraunfelder and Hanna (1973) distinguished between corneal and conjunctival degeneration, and subdivided the former into primary and secondary. The primary degeneration was located only in the periphery of the cornea, while the secondary was always, or almost always, associated with other ocular and, more specifically, corneal lesions. In the present study the finding that changes in the intermediate and central corneal zones were identical and continuous with the early peripheral changes, even in eyes without other corneal lesions, suggests that a classification confining primary degeneration to the corneal periphery is unsatisfactory. Seemingly a classification based on visual acuity will also be unsatisfactory because of the possible reduction of acuity by causes other than droplet degeneration. In the present study, for example, nine or 10 cases out of 80 with mild droplet degeneration had reduced visual acuity from other causes (mainly onchocerciasis). For these reasons it might be better to refer to the changes as mild when only granularity and/or droplets are seen and severe when more advanced changes are present, and to specify the distribution in both cases.

Provided a good slit lamp is available and the examiner is searching for the condition there is no difficulty in diagnosing the slight and subtle changes of mild droplet degeneration of the cornea. However, when the cornea is more extensively damaged problems of differential diagnosis arise. It may even be impossible in certain cases, unless they have been studied longitudinally, to arrive at a correct diagnosis. Isolated central corneal opacities, even when in the typical band position, need not be related to limbal areas of granularity and droplets. However, the severe central changes represented in Fig. 5 may reasonably be supposed to share the same pathogenesis as the widespread mild changes in the fellow eye (Fig. 4). Notably, not one case in this series showed an 'uncomplicated' band opacity such as was described and illustrated by Bietti and others (1955) and Freedman (1965). Both cases in which frank yellow corneal nodules were present also showed vascularization of the cornea and damage to deeper ocular structures.

The cases of mild droplet degeneration seen in the present series corresponded very closely with most of those described by Freedman (1965) in Labrador and by the same author (1973a) in South Africa and Australia. The cases classed by Fraunfelder and others (1972) as primary spheroid degeneration of the cornea also seemed to correspond, although these authors described the spherules as having various shades of yellow to gold and they implied that the cornea between each spherule was initially clear. They made no reference to the typical fine granularity or to the clear area between the lesion and the limbus which were seen in Labrador and Cameroon.

The descriptions of the early stages of the disease as recorded from East Africa, the Red Sea littoral, and Saudi Arabia are less easy to follow and more difficult to correlate with our findings. Falcone (1954) referred to Bowman's membrane as having a turbid, granular appearance, while Rodger (1973) used the descriptive term 'veil' for the early changes. For Bietti and others (1955) the dystrophy was clearly distinguished from classical band-shaped degeneration by the fact that it began more or less in the centre of the cornea and always at a considerable distance from the limbus. However, they did not have the advantage of a modern slit lamp, and therefore could not have seen the subtle peripheral changes. In one of their biopsy specimens they described tiny hyaline droplets in or just deep to Bowman's membrane, and probably this would have shown as granularity or stippling with a modern slit lamp at high magnification.

There are few reports on the natural history of droplet degeneration, although Bietti and others (1955) described its development based on Guerra's observations in Eritrea during eight years, and Freedman (1965) mentioned changes in one case in Labrador after a year. Fraunfelder and others

(1972) referred to a number of patients followed-up for more than three years. Most remained fairly stationary, and when they progressed there was a slow spread in a semicircular pattern adjacent to the limbus. The present paper does not attempt to describe the development of these lesions, but the changes of onchocerciasis were followed for four years and from the initial rough sketches of droplet degeneration it appears that changes had not been marked over this period.

Most authors have invoked climatic factors in the pathogenesis of droplet degeneration. In this connexion the condition was also looked for in the rain-forest zone of Cameroon during a large-scale onchocerciasis survey of over 600 patients. In the rain forest the sky is overcast for much of the year and exposure to bright sunlight is much less than in the savanna of north Cameroon. There is also less dust and sand in the rain-forest atmosphere and nothing to compare with the dust storms and desiccation that occur in the north. Interestingly, therefore, only one or two mild cases of droplet degeneration were found among the elderly in the rain-forest. The corneal changes of onchocerciasis in Cameroon were also much more pronounced in the savanna than in the rain-forest, and the more severe grades of sclerosing keratitis were confined to the savanna (Anderson and others, 1974). Thus, by analogy with our findings on droplet degeneration, it seems that climate, and especially exposure to sunlight, should also be considered as one of the many factors that may contribute to the regional differences found in ocular onchocerciasis.

Although the prevalence of onchocerciasis was high in cases of droplet degeneration it was equally high in cases without, and there was no correlation between the intensity of infection with *O. volvulus* and the prevalence and severity of droplet changes.

In his study of droplet degeneration (Labrador keratophy) Wyatt (1973) found mild changes in 28 out of 47 men aged 40 and over (60 per cent) in Labrador, while the same observer, presumably using the same examination and survey techniques, recognized it in only 21 out of 320 (7 per cent) men aged 40 and over in the Canadian north. The most severe grade was absent from the latter area, whereas it was seen in 9 of the 47 men examined in Labrador. An obvious difference between the two areas is in the amount of exposure to ultraviolet light, and more research is required on the effects of actinic radiation on the human cornea (Klintworth, 1972; Rodger, 1973).

An association between droplet degeneration and pterygium and pinguecula has often been commented on, particularly with reference to pathogenesis. In the series of Bietti and others (1955) pterygium was rare, while in Labrador signs of droplet degeneration were conspicuously absent in patients with active pterygium (Freedman, 1965). Rodger (1973) found pterygia twice as commonly in patients exhibiting Bietti's dystrophy, and Young and Finlay (1975) found an association between droplets and pinguecula and pterygium. However, they failed to explain the higher prevalence of pterygium on the nasal side compared with the equal nasal and temporal distribution of droplet degeneration. In the present study the finding that pterygium was equally common in persons with or without droplet degeneration supports the view that the two conditions, both commoner in older persons, are not otherwise related.

Globular hyaline deposits in the superficial stroma and epithelium of the cornea, which clinically resemble oil droplets, are often observed in association with other corneal disorders, such as post-traumatic scarring (Garner, 1969). The nature of their formation is still obscure (Hanna and Fraunfelder, 1972), as is their ultrastructure (Garner and others, 1973), and this has led to disagreements among clinicians and pathologists about the terminology which should be adopted (Fraunfelder and Hanna, 1973; Garner, 1969; Freedman, 1973a; Rodger, 1973). There is also difficulty in accepting under one heading all the mild and severe changes hitherto described. These difficulties will be resolved only by intensive epidemiological studies in different parts of the world.

Summary

The prevalence of droplet degeneration of the cornea in a defined population of 517 persons in north Cameroon was similar in males and females, but severe changes were commoner in elderly men. Most cases showed only mild changes of granularity and droplet formation in Bowman's zone, but they were sometimes widespread. More severe changes were seen in only nine patients. The clinical appearances are compared with those described from other parts of the world. In support of the aetiological role of direct sunlight, droplet degeneration was much more prevalent in the savanna than in the rain-forest in Cameroon.

The condition ranges in severity from very mild to very severe, but difficulties in differential diagnosis, particularly in advanced cases, make it doubtful whether the same basic condition is being described in all cases. These doubts will be resolved only by properly conducted epidemiological studies in different parts of the world.

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Fitting contact lenses after keratoplasty

R. DANIEL
From Moorfields Eye Hospital, High Holborn, London

The treatment of keratoconus parallels the progression of the cone. At first spectacles may be satisfactory, but as the cone worsens corneal and, later, scleral contact lenses are required to maintain satisfactory vision. In the advanced stage, when a contact lens can no longer be tolerated or an adequate visual acuity cannot be attained, keratoplasty is indicated. Hopefully, this is the final solution, but often it is not. Even when a clear corneal graft results the patient may still require spectacles or contact lenses to achieve reasonable vision.

Usually the result of penetrating keratoplasty for keratoconus is favourable. Castroviejo (1966) stated that a transparent graft and functional improvement should be expected in 90 per cent of cases. In this paper the outcome in cases of keratoconus treated with penetrating keratoplasty at the contact lens department, Moorfields Eye Hospital, is reviewed.

Patients and methods

One hundred cases in which penetrating keratoplasty resulted in clear grafts were reviewed. Cases that had developed eye complications (10 per cent) and those that resulted in less than 6/18 vision were considered to be unsuccessful and were excluded from the study.

The keratoplasties were of 7 mm diameter in three-quarters of the cases and of 8 mm diameter in the remainder. The smaller graft was preferred but was used only if the cone could be completely excised and the line of incision would not pass through the pupillary area. There was no significant difference in the corneal astigmatism resulting from a 7 mm graft than that from an 8 mm graft, and there was no significant difference in the final visual acuities. The surgical technique was similar in all cases except for the method of suturing with Perlon monofilament nylon, which was used as a continuous suture in some cases and as a continuous suture in conjunction with four interrupted sutures in others. Interrupted sutures were removed between one and three months after operation, depending upon the amount of corneal vascularization and the patients' comfort. Continuous sutures were not removed before three months after operation.

All of the patients had worn contact lenses, mostly scleral lenses, before keratoplasty. The indication for a corneal graft was poor visual acuity (6/18 or less) in 40 per cent of cases and the inability to wear contact lenses owing to intolerance or insurmountable fitting problems in 60 per cent. Two-thirds of the patients were men and one-third were women. Contact lenses were fitted without hesitation after keratoplasty in cases that required them.

Results

The visual acuities attained in the 100 eyes are shown in Fig. 1. These acuities were those achieved with the visual aid preferred by the patient—spectacles, corneal contact lenses, scleral contact lenses, or no aid at all. Therefore they were not necessarily the best acuities attainable but were the best that the patients could accomplish for everyday use without undue discomfort. Forty-one patients preferred a corneal contact lens (Fig. 2). The types of lenses prescribed are shown in Table I.

The visual acuities attained by the various aids are shown in Table II.

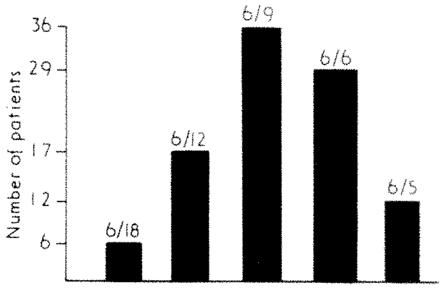

FIG. 1 *Visual acuities attained in 100 eyes after keratoplasty*

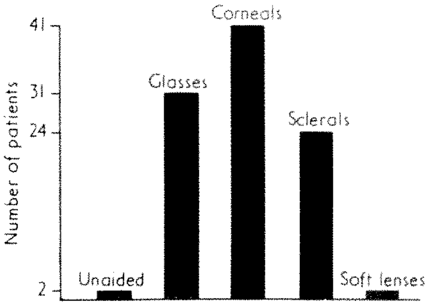

FIG. 2 *Visual aid preferred by the patient in 100 cases after keratoplasty*

Address for reprints: R. Daniel, FRCS, Moorfields Eye Hospital, High Holborn, London WC1

Discussion

Since most corneal grafts result in some corneal irregular astigmatism contact lenses are often required for satisfactory vision. They are also useful in the early postoperative period as a protective membrane, to compress or mould low rigidity grafts, or to realign grafts. Since the graft may take several months to become as rigid as the normal cornea splinting or moulding can start when the sutures are removed. Scleral shells are best for this purpose and they can be retained until the curvatures of the graft are consistent with good acuity. This technique is restricted to selected cases as neovascularization commonly results owing to the often poor ventilation. The scleral shells are prepared from an impression of the anterior segment of the eye obtained by injection technique. Refitting is necessary as the keratoplasty changes its contour or the operative oedema resolves. This method is particularly suitable for grafts that are proud of the host cornea or when tilting is excessive.

Soft contact lenses may be used for splinting, compression, or reducing ocular discomfort at an early stage, even before the sutures are removed. They can be worn constantly for several weeks without apparently affecting the nutrition or respiration of the graft tissue. Several cases in this series were fitted with large, flat-fitting soft lenses (85 per cent water content) at the end of the graft operation. In a few cases soft lenses were fitted at a later stage to try to alleviate ocular discomfort and blepharospasm due to graft sutures.

Table I *Types of corneal lens prescribed in* 41 *cases after keratoplasty*

Type of lens	*No. of cases*
C_4-toric periphery	2
C_4	4
C_3-toric periphery	5
C_3	15
C_2-toric periphery	4
C_2	—
C_1	1
Offset	8
C_2-bitoric	2
Total	41

Table II *Visual acuities attained with various aids in* 100 *eyes after keratoplasty*

Visual aid	*No. of eyes with visual acuity of*				
	6/18	6/12	6/9	6/6	6/5
Unaided	—	—	1	1	—
Glasses	—	4	13	9.	5
Corneal lens	4	7	11	14	5
Scleral lens	2	6	9	5	2
Soft lens	—	—	2	—	—

The final astigmatism and visual acuity were not noticeably better in cases of splinting with soft lenses. In some cases the soft lenses had to be removed prematurely owing to undue discomfort, and they did not substantially relieve blepharospasm or ocular discomfort from sutures or epithelial oedema.

Contact lenses for optical reasons may be fitted at any time after the removal of sutures. Corneal lenses, in fact, may be satisfactorily fitted and be tolerated in the presence of continuous corneal suturing, although, of course, they should not be fitted until inflammation has resolved. Neovascularization in the host tissue is not a contraindication to fitting lenses. Corneal irregularity resulting from keratoplasty usually lessens during the few months after the removal of sutures. Therefore it is advantageous to await stable keratometry before fitting contact lenses. Corneal lenses should be tried first in all cases, but in general they are more satisfactory with large grafts or with smaller grafts when the alignment between graft and cornea is good. When alignment is poor or astigmatism is high a thin corneo-scleral lens may be necessary, but if there is gross irregularity of the cornea a scleral lens is probably required. A lens of fairly rigid soft material can be used when there is intolerance to hard material. Intolerance, however, is not usually a problem after keratoplasty as the eyes are less sensitive and also the patient is usually strongly motivated.

Owing to the variety of the problems encountered the procedure for fitting corneal lenses after keratoplasty must be flexible and imaginative (Ruben, 1975). The cases with a fair degree of astigmatism, and therefore the more difficult to fit, are usually those that require contact lenses. Other problems in addition to the astigmatism often make fitting difficult. These may include poor alignment of the graft, protrusion of the graft, roughness of the graft-host junction, neovascularization and patches of oedema, and dry spots. Fitting must be by trial and error, which, unfortunately, may prove tedious and many lenses with various base curves and diameters may need to be tried. Often the trial-set lens fits the irregular corneal contour so poorly that an initial lens with the required modifications of the peripheral curves has to be ordered as a further trial lens.

In this series spherical lenses were fitted when possible regardless of the prevailing amount of astigmatism. A reasonable lens to start with is one with a base curve the same as the mean keratometry reading and of 9 mm overall diameter. All the lenses in this series were larger than the grafts. Lenses smaller than the grafts can be fitted but, owing to their small size, they are usually unstable and uncomfortable. Small lenses may also damage the graft-host junction, which is usually slightly raised. A larger lens rides with its edge outside the graft. The major problems in fitting lenses after keratoplasty are: difficulty in achieving stabilization in an acceptable position; difficulty in preventing the lid from flicking the lens out, especially with protuberant grafts; and the need to avoid problem areas.

When fitting, the lens should stabilize between blinks to a position over the graft. The optimal position is where the lens edge is furthest from potential trouble spots, which include the graft-host junction and areas of neovascularization, marked irregularity, oedema and scars around suture tracts, and chronic punctate staining. Obviously, compromises must be made to achieve the best fit and at the same time to avoid the trouble spots. In trying to stabilize the lens the usual basic principles apply, such as that steepening the base curve or increasing the diameter will increase the attraction of the lens for the cornea. The irregular surface of the cornea in these cases reduces the lens-cornea attraction and a larger lens is required to compensate for the loss in stability. However, the corneal irregularities allow an improved tear exchange and so larger lenses can be accepted more easily. Lenses with toric back surfaces are often needed to obtain the desired positioning and stability. Care must be taken to ensure that the edge lift is not too great, especially with proud grafts, in order to prevent the lens from being flicked out with the lid.

These patients may wear corneal lenses for up to 15 hours daily, preferably with a mid-day break, but they should be fairly closely watched since the usual warning symptoms of an ill-fitting lens are not normally felt after a keratoplasty. The lenses often need to be modified or changed frequently to overcome various problems that arise, especially in association with trouble spots already listed. The keratometry is also likely to change over the year or so after grafting. The two main complications that arise are neovascularization and oedema at the graft-host junction.

A wide range of lens types are required to satisfy the various criteria for the different eyes. In this series the tricurve spherical lens was used in 15 cases and the offset lens in eight (Table I). Toric peripheral curves were required in 13 lenses, two of these being bitoric. The toric peripheral curves were necessary to attain stabilization in the correct position by obtaining a better lens-cornea relationship than was possible with spherical curves. The overall diameter of nearly all the corneal lenses fitted in this series was between 9 and 9·5 mm and the centre thickness was 0·1 mm.

When irregularities of the cornea after keratoplasty are gross a corneal lens may be impossible to fit or the resulting visual acuity may be unsatisfactory. A fenestrated scleral lens is then indicated. Because of the toric cornea too large an air bubble often forms under these lenses and interferes with tear exchange or obscures vision. In these cases flush-fitting or channelled scleral lenses should be supplied.

Soft lenses may be used to improve the visual acuity after keratoplasty, and they are especially useful for patients who cannot tolerate hard lenses. The results are usually disappointing owing to the residual astigmatism, but this can be reduced by using the more rigid soft materials. Supplementary spectacles with the appropriate cylindrical lens can be used with the soft lenses to correct the residual astigmatism. In this series two patients settled for soft lens correction and both achieved 6/9 vision. One patient required supplementary spectacles and the other did not.

Summary

Even when a clear corneal graft results from keratoplasty spectacles or contact lenses may still be needed for reasonable vision. In a series of patients treated at the contact lens department, Moorfields Eye Hospital, a transparent graft and functional improvement resulted in about 90 per cent of cases. One hundred of these successful cases are reviewed and the problems of achieving a reasonable visual acuity for the patients discussed. Of those who needed a visual aid 41 preferred a corneal contact lens. The particular difficulties of fitting these are reviewed and the need for a flexible procedure to meet the varying circumstances emphasized. The methods adopted in the cases under review are described. In the 100 eyes visual acuities of 6/6 were attained in 29, 6/9 in 36, and 6/12 in 17.

I am grateful to Mr M. Ruben of Moorfields Eye Hospital for kindly allowing me to report on patients under his care.

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Simple method of determining the axial length of the eye

E. S. PERKINS, B. HAMMOND, AND A. B. MILLIKEN
From the Department of Experimental Ophthalmology, Institute of Ophthalmology,
University of London

The *x*-ray method of determining the axial length of the eye employed by Sorsby (Rushton, 1938; Sorsby and O'Connor, 1945; Duke-Elder and Abrams, 1970) has been superseded by ultrasonic techniques. Although the latter have attained considerable accuracy they can hardly be used for routine clinical purposes, particularly in children. The following method was developed to fulfil this need.

If the globe can be considered as a sphere rotating about a fixed point in a cup of orbital fat the movement of a point on the cornea during rotation of the globe through a known angle will be directly related to the radius of rotation. In Fig. 1 the eye rotates through an angle α about C to fix an object first at A and then at B. If the distance between X and Y can be measured and the angle α is known the radius of the globe CX or CY can be calculated thus:

$$CX = \frac{XY}{2 \times \text{sine } \alpha/2}$$

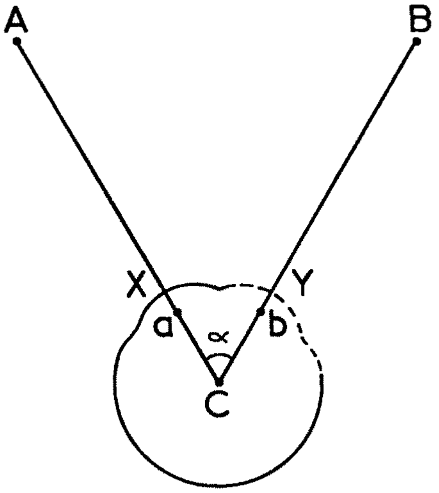

FIG. 1 *When eye rotates from fixation point A to fixation point B through known angle α movement of point on cornea from X to Y will be directly related to radius of rotation*

There are two important assumptions which require further examination. First, can the eye be considered to be spherical? This may be assumed to be almost correct for a normal eye. Although the radius of curvature of the cornea is less than the radius of curvature of the globe, the apex of the cornea is said to coincide with the circumference of the globe (Duke-Elder and Wybar, 1970), so that measurement of the radius from a point near the centre of the cornea to the centre of the globe will be equal to the radius of the globe. Doubling this measurement will give the axial length. In the case of a highly myopic eye, in which the globe is not enlarged symmetrically but which is elongated in its antero-posterior axis, rotation will take place about the centre of curvature of the posterior segment, and the distance from this point to the apex of the cornea will be greater than the radius of the posterior segment. A measurement derived from movement of a point on the apex of the cornea will not, therefore, give the radius of the posterior segment of such an eye, and doubling this measurement will give an overestimate of the total length. If, however, the method is used to estimate the progressive increase in length of an individual eye the increase in the distance from the apex of the cornea to the centre of rotation of the posterior segment will indicate the elongation of the eye. Although therefore such an estimation of the axial length may be inaccurate in a highly myopic eye the method will still give relevant information concerning the change in antero-posterior length in any individual eye.

The second assumption is that the globe rotates about a fixed point. The centre of ocular rotation in the horizontal plane was carefully measured by Park and Park (1933), who found from measurements on 14 subjects that as the eye rotated from 39° nasally to 38° temporally the centre of rotation moved along a curve slightly nasal to the visual axis and extending from a point 14·732 mm to a point 12·950 mm behind the cornea. At 4° nasally

Address for reprints: Professor E. S. Perkins, Department of Experimental Ophthalmology, Institute of Ophthalmology, Judd Street, London WC1H 9QS

the distance from the cornea was 13·918 mm, and at 3° temporally 13·749 mm. The antero-posterior movement of the centre of rotation was almost symmetrical about its position when the eye was in the primary position. If the centre of rotation is calculated from a symmetrical position a mean value would be obtained which, although not from the exact geometric centre of rotation, would be comparable from one eye to another.

There are therefore some theoretical objections to a calculation of the radius of the globe from observations of the movement of the apex of the cornea, but as the method is simple it seemed worth trying in the hope that measurements of clinical value could be obtained.

It is impossible to visualize the apex of the cornea for purposes of measurement, and observation of a small feature such as a blood vessel at the limbus was found to be difficult. However, if the fixation points A and B in Fig. 1 are replaced by illuminated targets in the form of a slit a bright corneal reflex can be seen and photographed by means of a camera mounted between A and B. The reflection of the target lies on the visual axis behind the cornea and its position depends on the corneal curvature. It would be possible to measure the corneal curvature (and hence to determine the position of the image) by using a keratometer, but if the targets at A and B are photographed simultaneously the corneal curvature can be obtained from the separation of the two images (A and B in Fig. 1) either by calculation or by means of a calibration curve obtained by photographing a series of polished steel balls of known radius. The latter method is more convenient, as an allowance can be made for the magnification of the photographic image and the actual distance between the two images on the film can be plotted against corneal curvature.

Method

The apparatus employed is shown diagrammatically in Fig. 2. The reflex camera, fixation targets, etc., were mounted on a slit-lamp base placed on an instrument table. The targets were arranged on an arc, the centre of curvature of which was the focal point of the camera lens, and separated by an angle of 40° or 60°. The lens was an 80 mm Leitz Photar mounted on an extension tube which contained a small fibre-optics light guide mounted 94 mm behind and facing the lens. This provided a fixation spot for the patient during keratometry.

The subject was seated with his head on the head-rest and instructed to look at the lens of the camera. In addition to a constant illumination of the test target—a slit—from a festoon bulb, a small flash tube, was placed behind each target. The images of the targets could be accurately focused by moving the instrument with the joystick of the slit-lamp base, and a photograph of the cornea was taken with both targets illuminated by the flash tubes. The subject was then instructed to look at a red dot in the centre of the left-hand target and another photograph taken with the flash from this target. The shutter of the camera was kept open and the subject viewed a green dot in the centre of the right-hand target while this flash was fired. The resultant frame had a photograph of the eye in the two positions of gaze, and the image of each target appeared separated by a distance which could be measured and used to calculate the radius of movement of the reflex. Photographs of each eye were taken twice.

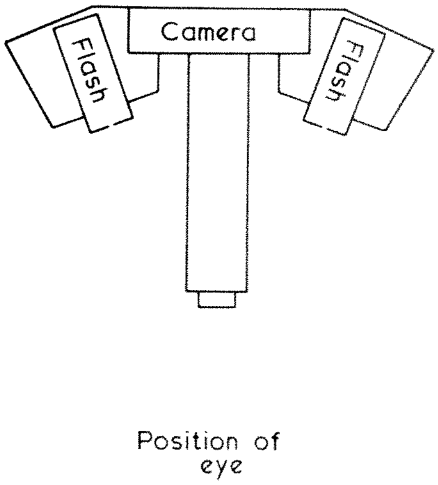

FIG. 2 *Diagram of apparatus for photographing bright corneal reflexes from fixed flash targets*

It was found convenient to place a scale calibrated in fifths of a millimetre in front of the film plane, so that an image of the scale was also obtained on the film and the separation of the reflexes could be read direct from the negative. So that the background exposure of the film would be sufficient to show the scale, the shutter was used in the 'bulb' position and kept open for about 5 s. With FP4 film the scale could be seen clearly on each frame. A switch was provided so that in one position both flashes were fired simultaneously for measurement of the corneal radius and in the second position either flash could be fired by pressing one of two buttons. This was probably an unnecessary refinement, as even if both flashes were fired with the eye in the two positions of movement it was easy to see on the film which of the two flashes was aligned with the optic axis.

CALCULATIONS

Keratometry

Knowing the magnification of the camera (× 1·875), it was possible to derive the separation of the two images in millimetres and from this measurement to calculate the radius of curvature, knowing the actual distance between the two light sources and their distance from the cornea.

From a series of tests on steel ball-bearings of known diameter it was found that no serious error was introduced by multiplying the separation in millimetres of the images on the film by a constant factor of 1·62, and this was used for the clinical measurements.

Radius of movement of globe

From Fig. 1 it can be seen that the image of targets placed at A and B will lie on the optic axis behind the surface of the cornea. Its position on the optic axis will depend on the curvature of the cornea and the distance between the cornea and the target. If the target is at infinity the image will be at the focal point—that is, halfway between the centre of curvature of the cornea and the corneal surface. In this apparatus the target is not at infinity and, although the position of the image could be calculated, for clinical purposes the narrow slit can be considered as a point source and the calculations simplified by considering it to be at infinity.

The separation of the two images on the film is corrected by the magnification factor (×1·875) and the radius of their movement as the eye moves from one target to the other equals their linear separation in millimetres divided by the sine of the angle of movement (usually 40°). To obtain the radius of the globe the distance of the image from the anterior surface of the cornea has to be added to the radius of movement of the images.

Results

To test the method steel balls of known radius from 6·35 to 8·73 mm were mounted on a pivot in such a way that they could be rotated with varying centres of rotation through an angle of 60°. The face of the balls thereby represented the corneas of eyes of different diameter. The radii of rotation were in the range expected in human eyes and varied from 11·35 mm to 15·33 mm, representing axial lengths of 22·7 mm to 30·66 mm.

The results (Table I) showed that there was fairly good agreement between the so-called true radius of rotation and that calculated from the photographs. The 'true radius' consisted of an accurate measurement of the steel ball with a micrometer added to its distance from the centre of rotation of the pivot—normally 5, 6, or 7 mm, although this distance could not be measured so accurately as that of the diameter of the balls. The mean error between the 'true radius' and the measured radius was −0·11 mm (SD 0·11, SE 0·0213).

Clinical measurements

Measurements were made on 80 eyes of patients aged 10 or over. As expected, the axial length of eyes with small refractive errors (+2·00 D to −1·00 D) showed no significant correlation with axial length. The mean for male eyes was 27·95 mm and for female eyes 26·33 mm.

Table I *Verification of photographic measurements using steel balls of known radii rotated through known angles*

Radius of ball (mm)	*True radius of movement (mm)*	*Measured radius (mm)*	*Difference*
6·35	11·35	11·49	+0·14
6·35	12·35	12·59	+0·14
6·35	13·35	13·10	−0·25
6·74	11·74	11·71	−0·03
6·74	12·74	12·84	+0·10
6·74	13·74	13·82	+0·08
6·99	11·99	11·91	−0·08
6·99	12·99	12·83	−0·16
6·99	13·99	13·80	−0·19
7·14	12·14	12·16	−0·02
7·14	13·14	13·07	−0·07
7·14	14·14	14·05	−0·09
7·52	12·52	12·40	−0·12
7·52	13·52	13·53	+0·01
7·52	14·52	14·47	−0·05
7·92	12·92	12·60	−0·32
7·92	13·92	13·66	−0·26
7·92	14·92	14·49	−0·36
8·00	13·00	12·89	−0·11
8·00	14·00	13·80	−0·20
8·00	15·00	14·81	−0·19
8·35	13·33	13·23	−0·10
8·33	14·33	14·25	−0·08
8·33	15·33	15·32	−0·01
8·73	13·73	13·59	−0·14
8·73	14·73	14·62	−0·11
8·73	15·73	15·60	−0·13
9·00	14·00	13·89	−0·11
9·00	15·00	14·80	−0·20
9·00	16·00	15·79	−0·21

Mean error −0·11, SD 0·11, SE 0·0213

Fig. 3 shows the refraction of all eyes plotted against their axial length. There is an obvious correlation, and computer analysis gave a correlation coefficient for all eyes of −0·8592. The regression line for axial length on refraction was R= −2·578 A + 66·658, where R=refraction in dioptres and A=axial length in millimetres. The correlation for female eyes alone (Fig. 4) was −0·7607 and for male eyes (Fig. 5) −0·8925. If eyes with refractions between +2·00 D and −1·00 D were excluded the correlation coefficient was −0·8739. There was also a correlation between corneal radius and refraction (−0·2012 for all eyes) (Table II).

Discussion

The axial length of eyes with low refractive errors as measured by this method is about three milli-

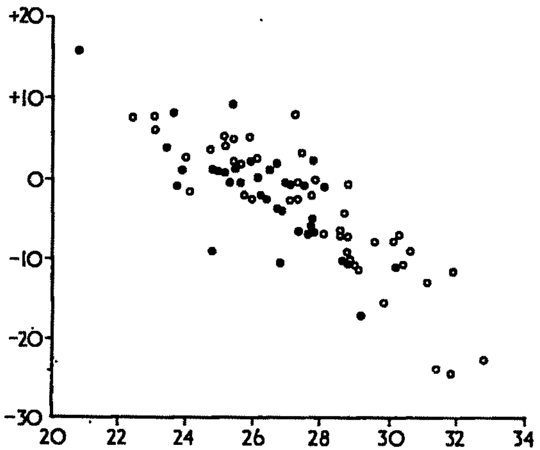

FIG. 3 *Measurements of axial length plotted against refractive error in* 80 *eyes*

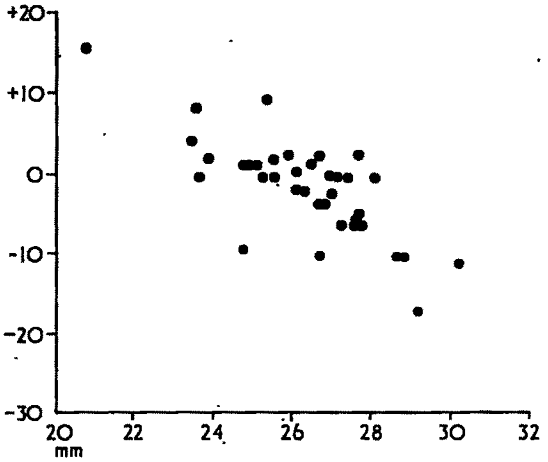

FIG. 4 *Measurements of axial length plotted against refractive error in* 37 *female eyes*

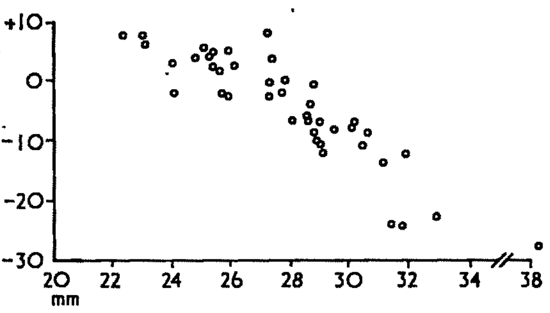

FIG. 5 *Measurements of axial length plotted against refractive error in* 43 *male eyes*

Table II *Correlation coefficients*

Coefficients between	*Female eyes*	*Male eyes*	*All eyes*
Refraction and axial length	–0·7607	–0·8925	–0·8592
Refraction and corneal radius	–0·1135	–0·2555	–0·2012

metres greater than that obtained by *x*-ray or ultrasonic techniques. The latter techniques measure the distance between the anterior surface of the cornea and the retina, whereas the present method includes the thickness of the choroid and sclera. According to Duke-Elder and Wybar (1970) the choroid is 0·2–0·3 mm thick and the sclera 1–1·3 mm thick at the posterior pole, so our measurements would be expected to be about 1·5 mm too great. This still leaves 1·5 mm to be accounted for. The calculation of axial length assumes that the apex of the cornea coincides with the circumference of the globe. If, however, this assumption is incorrect and the cornea is a segment of a sphere protruding from the globe the axial length as calculated would be overestimated by the corneal protrusion. Assuming a corneal radius of 7·5 mm, a corneal diameter of 12 mm, and a radius of curvature of the globe of 12 mm it can be calculated that the distance from the centre of rotation of the globe to the apex of the cornea is 1·43 mm greater than the radius of curvature of the sclera.

Park and Park (1933) found the centre of rotation of the globe to be about 13·8 mm posterior to the apex of the cornea, which is similar to the mean value in male emmetropic eyes in our series. This adds support to the suggestion that the apex of the cornea does not lie on the circumference of the globe but protrudes beyond it.

The correlation between the axial length, as measured by the present method, and the refraction is similar to that obtained by Stenström (1948) by ultrasonography, and suggests that even if we are not measuring the true axial length of the eye the dimension measured is so closely related to the axial length that it is valid for clinical purposes. The slope of the regression line for axial length/refraction is such that a change of refraction of 1·00 D is equivalent to a 0·39 mm change in axial length.

Some idea of the consistency of the readings may be obtained by comparing the paired readings of corneal radius and axial length made on each eye. The two measurements of corneal radius were identical in 52 of the 80 eyes, and differed by 0·05 mm in 13 and 0·10 mm in 12 eyes. As would be expected, the differences between the paired readings of axial length were greater; the measurements were identical in 13 eyes but differed by over 1 mm in eight eyes. Four of these eyes were highly myopic with poor fixation and two were highly hypermetropic, also with poor fixation. The mean difference between paired readings for 80 eyes was 0·43 mm.

In spite of the theoretical objections to this photographic method the excellent correlation between the measurements and refraction suggests that the method is a useful alternative to ultrasonography. In addition it is quick to do, comfortable for the patient, and does not demand expensive apparatus.

Summary

By photographing the corneal reflex in two positions of gaze and measuring the radius of curvature of the cornea it is possible to calculate the radius of rotation of the eye. The measurements obtained in this way showed a high correlation with refraction in a series of 80 eyes. The axial length obtained by this method was about 3 mm greater than that obtained by ultrasonographic or *x*-ray methods, and the reasons for the discrepancy are discussed.

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Early and late results of fascia lata transplantation in high myopia

A. P. NESTEROV, N. B. LIBENSON, AND A. V. SVIRIN
From the Department of Eye Diseases, 2nd Moscow Medical Institute, USSR

In 1970 we described the technique and preliminary results of strengthening the sclera with a strip of fascia lata in progressive myopia (Nesterov and Libenson, 1970). However, our follow-up was limited and the final results were uncertain. The present paper analyses the early and the late results in a group of myopic patients who were followed-up for periods of up to 9 years.

Patients and methods

The operation was performed on 184 eyes of 108 patients aged from 8 to 52 years. The degree of myopia varied from 7 to 39 dioptres (mean 18 D), 78 eyes were astigmatic (more than 1·0 D cyl.), and 70 had profound degenerative changes of the choroid and the retina. The myopia was definitely progressive in 128 eyes. Reliable information on whether the myopia was progressive or stable was not available in the remaining cases.

Our operation is a modification of that of Shevelev (1930) and Curtin (1961). The technique has been reported in detail elsewhere (Nesterov and Libenson, 1970). Briefly it is as follows. With a fascial stripper a strip of fascia lata 120 mm long and 6 mm wide is excised through a 30 mm incision in the outer surface of the thigh. The strip is cut longitudinally to make a Y-shaped transplant with one broad and two narrow arms. The conjunctival-tenon incisions are made in the superonasal, inferonasal, and temporal quadrants of the eyeball. The lateral rectus muscle is then cut off. With the help of a Curtin hook (Curtin, 1961) the graft is placed behind the globe, its narrow arms running above and below the optic nerve and then through the superonasal and inferonasal incisions. The third, broad arm runs along the horizontal meridian at the temporal side. Each of the arms is fixed to the sclera by two silk sutures. The lateral rectus is resutured to the globe and the conjunctival-tenon incisions are closed with running silk sutures.

Results

1. EARLY

Three to 4 weeks after the operation visual acuity without correction had improved by 0·02 to 0·14 (mean 0·08) in 171 eyes (93 per cent). Visual acuity with correction had improved by 0·1 to 0·2 in 106 eyes (58 per cent) and by 0·25 to 0·5 in 45 (24 per cent). In one eye, as a result of postoperative uveitis, visual acuity decreased by 0·06 without correction and by 0·3 with correction.

Visual fields were investigated by a kinetic technique with the hemispherical Kugel perimeter. The peripheral boundary of the field was examined (3/330) in 12 directions without glasses and both paracentral and central areas with corrective glasses (1/330). Either a concentric or sectorial narrowing of the visual field was found in 177 eyes. It became wider by 10 to 25 degrees in at least two directions in 160 cases after surgery. The changes in paracentral and central areas (70 eyes) were stable.

Refractive power was examined with a Hartinger refractometer and sciascopically. Myopia had decreased in 169 eyes (92 per cent) by 1 to 8 D (mean 3·1 D). The power of corrective glasses had decreased by zero to 8 D (mean 3·0 D).

2. LATE

Follow-up after operation was for periods of from 1 to 9 years in 105 eyes (67 patients): from 1 to 3 years in 56 eyes, from 3 to 5 years in 15, from 5 to 7 years in 27, and for more than 7 years in 7 eyes.

The results are summarized in the Table. Visual acuity had improved in 76 eyes (72 per cent).

Table *Late results of surgery in* 105 *myopic eyes*

	Improved		*Unchanged*		*Impaired*	
	No.	(%)	*No.*	(%)	*No.*	(%)
Visual acuity without correction	76	(72)	21	(20)	8	(8)
Visual acuity with correction	76	(72)	23	(22)	6	(6)
Degree of myopia	92	(88)	7	(6)	6	(6)

Address for reprints: A. P. Nesterov, Department of Eye Diseases, 2nd Moscow Medical Institute, Malaja Pirogovscaja Street, Moscow 435, USSR

The mean improvement was 0·05 without correction and 0·18 (0·03 to 0·4) with corrective glasses. The degree of myopia had decreased in 92 cases (88 per cent) by 0·5 to 8·5 D (mean 4·2 D). The power of glasses required decreased in 91 eyes by 0·5 to 6 D (mean 3·8 D).

The differences between the early and the late results were not notable in 64 eyes (61 per cent). The corrected visual acuity had increased by 0·03 to 0·2 in 35 eyes (33 per cent) and decreased by 0·02 to 0·15 in 6 cases (6 per cent).

Comparison of the changes in refractive power of the two eyes in those patients in whom only one eye was operated on was of interest. In 29 cases followed-up for 1 to 7 years the degree of myopia had risen in only five (17 per cent) by 0·5 to 3 D (mean 1·7 D). In the fellow eye the degree of myopia had increased in 24 cases (83 per cent). The average increase in refractive power was 2·9 D (range 1·5 to 6 D).

Retinal detachment occurred in only one of the 105 eyes. It was cured by surgery without any change in visual acuity or refractive power. There was no retinal detachment in 29 fellow eyes.

Discussion

The operative results in these cases show that the risk of complications is small. As a rule the operation halts the progress of the myopia or delays it for several years. In many cases the operation leads to both a decrease in the degree of myopia and an improvement of visual function.

The effect of the operation on the eye can hardly be limited to supporting the posterior sclera with the graft. Two other factors may be involved. Unexpectedly, we found that ocular tension was appreciably lowered after surgery. The mean (±SE of mean) applanation intraocular pressure in 184 eyes was 16·7±0·31 mmHg before surgery and 14·1±0·36 mmHg three weeks after surgery ($P<0·001$). In 42 eyes that were examined three years or more after surgery the intraocular pressure was 2·2±0·24 mmHg lower and the C-value 0·038±0·014 mm^3/min mmHg higher compared with their preoperative level. These differences are significant ($P<0·05$). The reason for the increase in the outflow facility and the decrease in the intraocular pressure is not clear. Perhaps the beneficial effect of the operation on myopia partly depends on a decrease in ocular tension.

Libenson (1967) showed experimentally that a strip of fascia lata transplanted to the eyes of rabbits led to the formation of new blood vessels both in the graft and the neighbouring scleral tissue. Improvement in the blood supply of the posterior sclera is believed to play a part in strengthening scleral tissue.

Thus, the beneficial effect of the operation seems to be due to the support given to the posterior sclera by the fascial graft, the lowering of ocular tension, and the improvement in the blood supply to the scleral tissue.

Summary

Transplantation of a strip of fascia lata to strengthen the posterior sclera in high progressive myopia was performed on 184 eyes of 108 patients with myopia ranging from 7 to 39 D. Three weeks after surgery visual acuity with correction had improved by 0·1 to 0·5 in 151 eyes (82 per cent) and refractive power had decreased by 1 to 8 D in 169 eyes (92 per cent). In 105 eyes (67 patients) that were followed-up for periods of from 1 to 9 years myopia increased in six by 0·5 to 3 D. In 29 patients who had an operation on only one eye and were then followed-up for periods of from 1 to 7 years the degree of myopia in the fellow eye increased by 1·5 to 6 D in 24 (83 per cent), and of the eyes that were operated on myopia increased by 0·5 to 3 D in only 5 (17 per cent).

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Visually evoked cortical potentials in the evaluation of homonymous and bitemporal visual field defects

H. G. H. WILDBERGER,* G. H. M. VAN LITH, R. WIJNGAARDE, AND G. T. M. MAK
From the Eye Hospital, Erasmus University, Rotterdam, The Netherlands

Ever since visually evoked cortical potentials (VECPs) were first used as a diagnostic aid the important question has been whether they could detect visual field defects. In earlier investigations (Vaughan, Katzman, and Taylor, 1963; Vaughan and Katzman, 1964; Kooi, Güvener, and Bagchi, 1965) light-flash stimulators illuminating the entire retina were used and the bioelectrical responses from both hemispheres were compared. Because asymmetries between the hemispheres were also found in normal people only differences of 50 per cent or more between the responses of the right and left hemisphere were considered significant. Later, methods of stimulating the temporal and nasal parts of the retina separately with flash and checkerboard stimulation were introduced (Cobb and Morton, 1970; Biersdorf, 1974). Finally, Regan and Heron (1969) devised a sophisticated method of separating the signals from retinal areas stimulated simultaneously. There are few reports of the clinical application of these techniques. This paper reports our experience in this field.

Patients and methods

Six patients with homonymous hemianopia (due in five cases to a vascular insult and in one case to a tumour in the parieto-occipital region) and six patients with a bitemporal hemianopia (all with a tumour in the region of the chiasm) were examined, the latter group both pre- and postoperatively. A projection system was used for the checkerboard-reversal stimulation. The screen subtended a 24° visual angle while the individual checksize was ½°. The modulation depth of the black and white squares was 90 per cent. The reversal frequency amounted to 8 Hz. During full-field checkerboard stimulation the patient had to fix a small spot in the centre of the illuminated screen. After that a half-field stimulation was applied by presenting only the vertical half of the original screen. In the latter the patient had to fix a small light attached to the right or left border just outside the stimulating field. A vertical strip to avoid possible interhemispherical callosal projections (Regan and Cartwright, 1970) was not used.

The electrodes were placed according to the EEG 10 to 20 per cent system. For our purpose we used a smaller distance for the electrode position in the midline—namely, 5, 15, and 25 per cent above the inion. From these both a bipolar and a referential lead were used. The bipolar registration was made from the 5 to the 25 per cent position and the referential registration from the 15 per cent position to the right earlobe, the left earlobe being earthed. Furthermore, two bipolar registrations were made from the right and left hemisphere—that is, from O_2 to C_4 and from O_1 to C_3.

In full-field stimulation the amplitude measured from the referential lead appeared to be normal in our set-up (above 7·5 μV), whereas in half-field stimulation only a difference in amplitude of more than 50 per cent between the hemispheres was considered significant. With a reversal frequency of 8 Hz we obtained steady-state VECPs, so we measured the phase instead of peak latencies. The latter can be measured only with transient VECPs obtained by low frequency stimulation (Halliday, McDonald, and Mushin, 1972). For the phase we measured the time between the trigger of the averager and the first positive peak of the sinusoidal response (marked by horizontal line in Figs 1 and 3). The normal values are within 118 ms ±9 ms.

In half-field stimulation the amplitudes and phases from the stimulated hemispheres were compared. On stimulating the right eye, for example, the response from the left hemisphere, arising from temporal half-field stimulation, was compared with the response from the right hemisphere, arising from nasal half-field stimulation (Fig. 2). These differences were more pronounced than those in the responses from the midline electrodes. Nevertheless, examination of normal individuals showed that a 50 per cent criterion had to be applied to them also. A difference of more than 10 ms in the phase was considered to be pathological.

Results

HOMONYMOUS HEMIANOPIA

Figs 1 and 2 show the VECPs in a 52-year-old patient after a cerebral vascular accident resulting

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Address for reprints: Dr G. H. M. van Lith, Eye Hospital, Erasmus University, Rotterdam, Holland

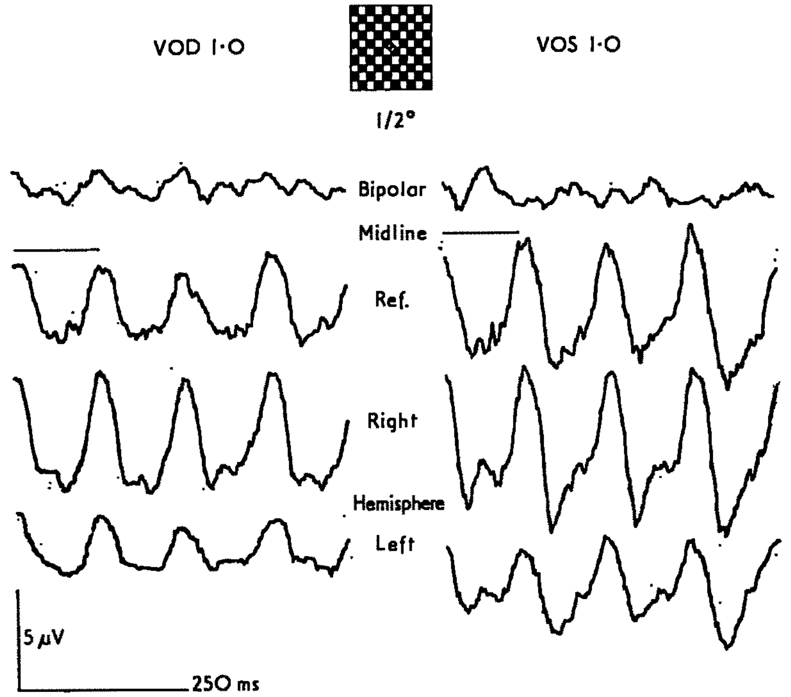

FIG. 1 *VECPs from right and left eye of patient with incomplete homonymous hemianopia to right. Full-field stimulation. Upper recordings are bipolar registrations in midline; second recordings are referential registrations from midline to right earlobe; third and lower recordings are bipolar registrations from right (R) and left (L) hemisphere. Phase marked by horizontal line above recording. In all figures upward deflexions indicate positive polarity*

in an incomplete homonymous hemianopia to the right without sparing of the macula. Full-field stimulation (Fig. 1) showed slightly reduced amplitudes, while the phase (horizontal line to the first peak of the referential response) was normal for both eyes. There was a marked difference in amplitude, however, between the hemisphere responses, indicating a left-sided cerebral disturbance. Temporal half-field stimulation (Fig. 2) gave from the right eye, in accordance with the visual field defect, much lower responses than nasal half-field stimulation. There was also a phase difference.

Differences in amplitude and phase were greatest between the responses of the directly stimulated hemispheres. A small response was obtained from the non-stimulated left hemisphere after nasal half-field stimulation. This response may have been transmitted by intercallosal connexions and may indicate that the seat of the lesion was not on a cortical level (Mitchell and Blakemore, 1970). The findings in visual field and VECPs in the left eye were of the same kind as those in the right eye.

Of the six patients examined only two showed slightly reduced amplitudes in the midline leads after full-field stimulation, while the phase was always normal. A 50 per cent difference in amplitudes between the hemispheres after full-field stimulation was present in three cases. With half-field stimulation a difference of more than 50 per cent was seen in four patients and of less than 50 per cent in one. One patient showed no difference; his visual field defects were peripheral.

BITEMPORAL HEMIANOPIA

Figs 3, 4, and 5 show the VECPs in a 63-year-old patient with a chromophobe adenoma. After full-field stimulation (Fig. 3) the amplitudes were obviously reduced on the left eye. A pathological phase shift (horizontal lines) was seen from both eyes. After full-field stimulation of the right eye the responses from the left hemisphere were smaller than those from the right; after full-field stimulation of the left eye the responses from the right hemisphere seemed to be somewhat more impaired. Half-field stimulation of the right eye (Fig. 4) again gave the greatest difference in amplitude and phase when the curves from the directly stimulated hemispheres were compared.

The result was clear although the visual field defect was limited only to the temporal superior quadrant of the two most inner isopters. After the operation the visual field defect became much smaller (Fig. 5). The difference in amplitude after half-field stimulation was about 30 per cent

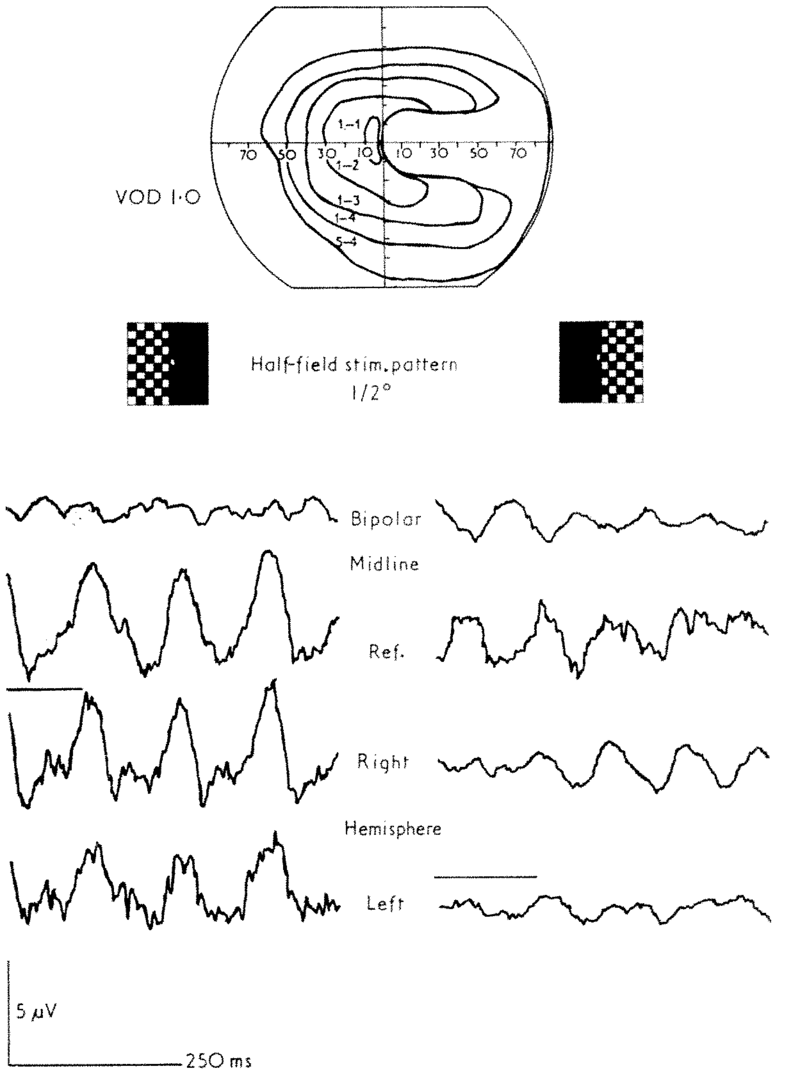

FIG. 2 *Homonymous hemianopia to right, same patient as in Fig. 1. Half-field stimulation of right eye. Responses from nasal half field on left, from temporal half field on right*

whereas the phase difference was still significant.

Even on the side where the visual acuity was not yet impaired reduction of amplitude and phase shift were the most important findings in our six patients when examined before the operation with full-field stimulation. The decrease in amplitudes were not so great when only quadrant field anopias were present. Even then significant differences could be found by half-field stimulation.

After operation the amplitudes remained reduced in half of the cases and in two patients showed a doubling of the peaks (Fig. 5, nasal stimulation), a phenomenon which is often seen in the recovery period of optic neuritis. The phase tended to return to normal from the less affected eye. The difference between the hemispheres after full-field stimulation or half-field stimulation remained when there was a large, persisting visual field defect.

Discussion

Earlier studies (Vaughan and others, 1963; Kooi and others, 1965; Oosterhuis, Ponsen, Jonkman, and Magnus, 1969) pointed out the difficulties in differentiating between normal variations in the flash VECPs and the abnormal, the latter appearing as a reduction of the early components (waves I,

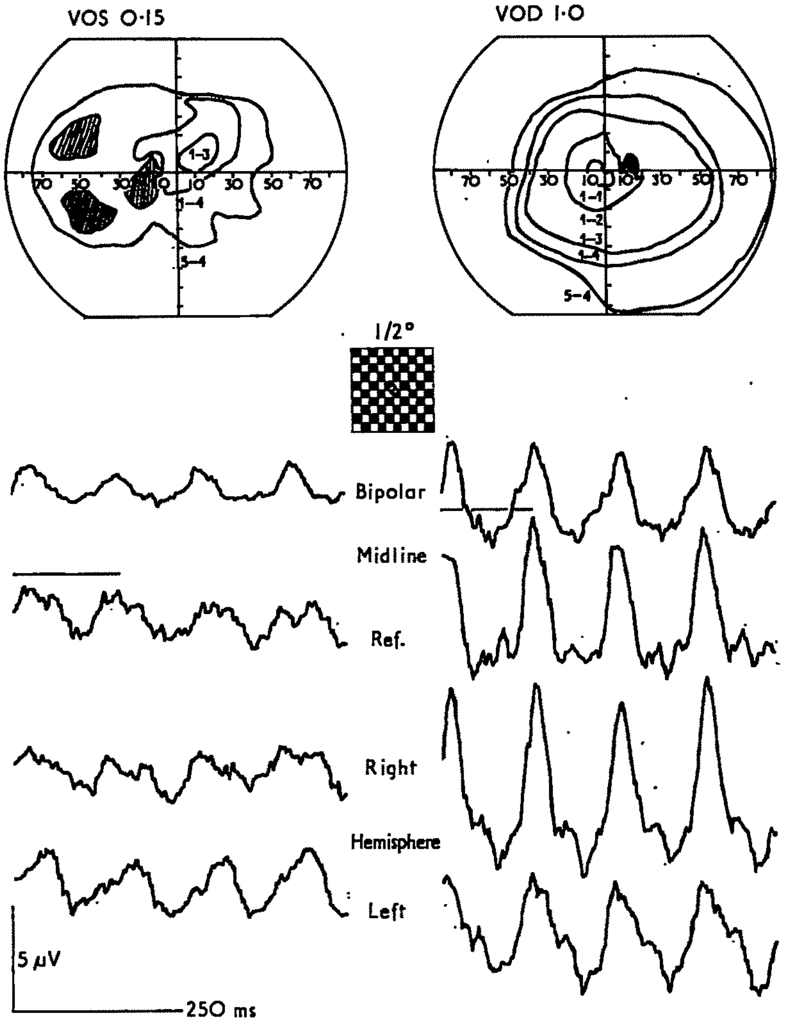

FIG. 3 *Preoperative VECPs from right and left eyes of patient with bitemporal hemianopia after full-field stimulation*

II, and III according to Cigánek's nomenclature). Although VECPs evoked by flash stimulation of low frequency cannot directly be compared with VECPs from pattern-reversal stimulation of a higher frequency ('steady-state' responses) as used in this investigation, our results are comparable with those in the studies referred to.

The difference between homonymous and bitemporal hemianopia is that in the latter the visual input is disturbed more at the periphery, whereas in homonymous hemianopia the site of generation of the VECP itself may be impaired. Oosterhuis and others (1969) concluded that the VECPs are not determined only by the visual pathways and the visual projection areas, since other regions may also be affected and abnormal EEGs may also influence the VECPs. Our investigations in homonymous hemianopia, however, did not support this view. The VECPs were probably not interfered with by influences from outside the visual system any more than in the case of bitemporal hemianopia.

The difference between cases of homonymous hemianopia, with and without macular sparing, was inapparent. Our mode of stimulation with rather large checksizes, producing a luminance component, stimulates the paramacular areas more, where the influence of pericallosal connexions is small. This means that the effects of our stimulus were similar to those of the sinusoidally modulated flicker used by Regan and Heron (1969), which is unable to detect macular sparing.

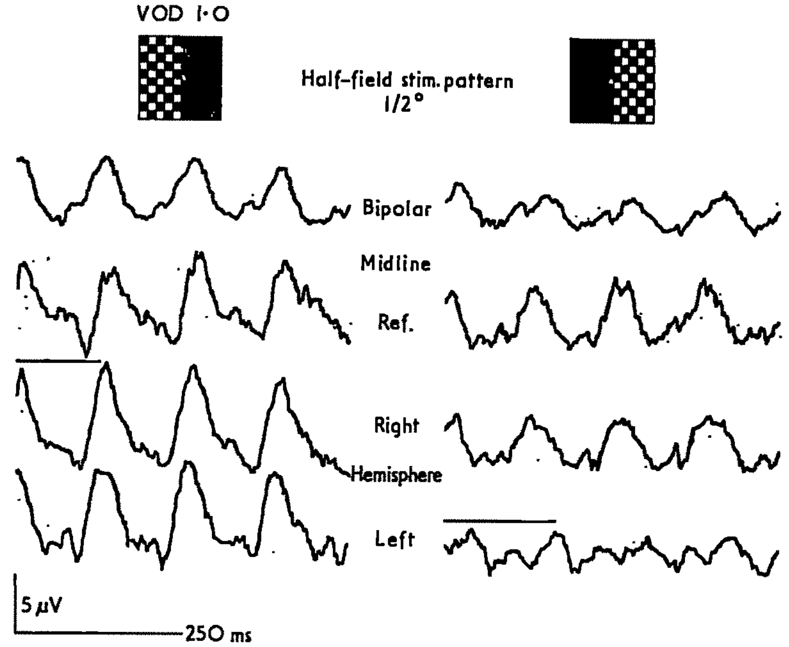

FIG. 4 *Same patient as in Fig. 3. Preoperative VECPs from right eye: nasal stimulation on left, temporal stimulation on right*

In bitemporal hemianopia, optic nerves and chiasm are often compressed to a thin cord. Obviously not only are the crossing fibres from the nasal retinae then impaired but also those from the temporal halves. This may occur with rather good nasal visual fields, whereas the VECPs are much reduced and delayed. Pressure of a tumour on the optic nerves may give various clinical pictures. When there is unilateral neuritis the VECPs are not of much help in differentiation. A clear-cut situation, as in the case of a split chiasm (Fisher, Jampolsky, and Scott, 1968; Lehmann, Kavanagh, and Fender, 1969) where the fibres from the temporal halves are intact, is seldom seen. In the acute stage of neuritis or pressure on the optic nerves the responses are often very low, near to the noise level (van Lith and Mak, 1974). In these cases differences in amplitudes or phases cannot reliably be measured.

Summary

Visually evoked cortical potentials were studied in six patients with a homonymous and six with a bitemporal hemianopia by presenting a pattern-reversal stimulus separately to a temporal or nasal retinal area and by recording the responses from leads over the hemispheres. Homonymous visual field defects are characterized by a reduction of VECPs from the affected hemisphere. The disturbance of VECPs in bitemporal hemianopia is more serious, since the fibres from both retinal halves may be damaged by a chiasm tumour.

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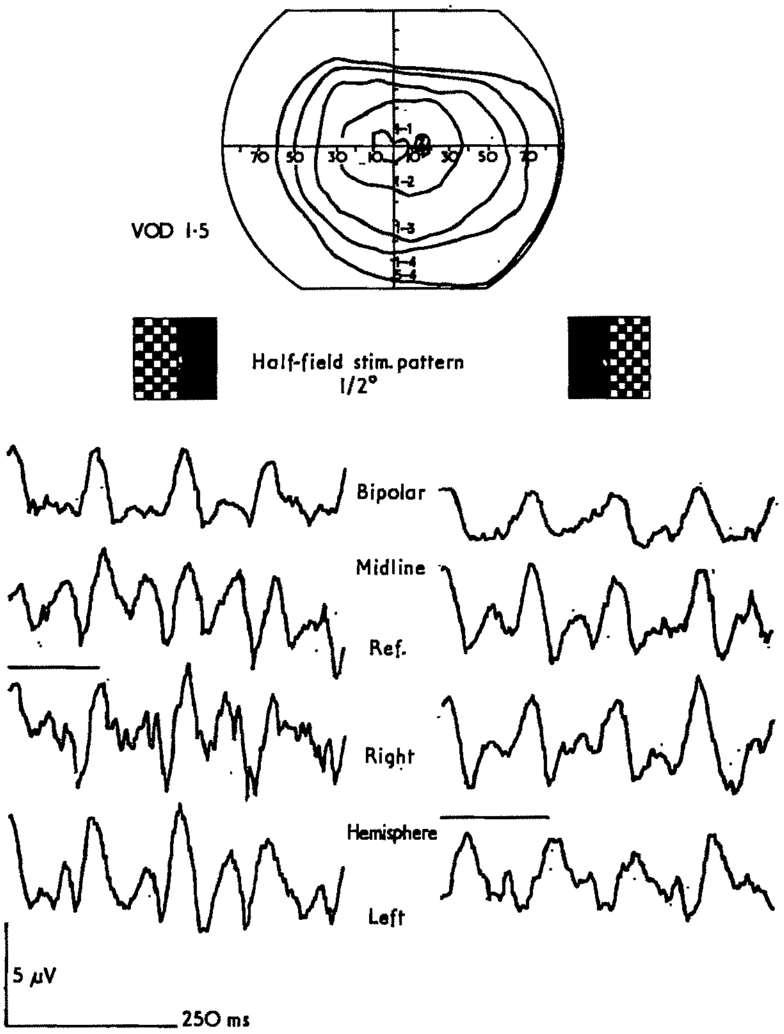

FIG. 5 *Half-field stimulation of same eye as in Fig. 4 after operation*

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Pseudoexfoliation of lens capsule and glaucoma
Case report

LEON CEBON AND REDMOND J. H. SMITH
From Moorfields Eye Hospital, City Road, London

A woman aged 80 years was first seen in October 1973. She had been suffering from watering eyes and on one occasion, when wiping her right eye, had noticed that the vision of her left eye was blurred. In the past she had had an operation on her 'tear duct', pyelitis, and an operation for an abdominal cyst. Currently she was well apart from some rheumatoid arthritis of her hands.

Examination showed her visual acuity to be right 6/5, left 6/60. The right lens capsule showed pseudoexfoliation (Fig. 1) while the left lens capsule was quite unaffected (Fig. 2). Gonioscopy showed wide open angles without trabecular pigmentation. The intraocular pressure was right 18 mm and left 24 mm. The right optic disc was normal but the left showed glaucomatous cupping and new vessel formation. There were also several retinal haemorrhages characteristic of retinal branch vein thrombosis. There were no other significant clinical findings. In short, the findings were of an old woman with pseudoexfoliation of the right lens capsule and no glaucoma, glaucoma of the left eye without pseudoexfoliation, and an absence of typical trabecular pigmentation in either eye.

Discussion

Pseudoexfoliation of the lens capsule was first noted by Lindberg (1917) and more fully described by Vogt (1925), who also noted its association with glaucoma and coined the term 'glaucoma capsulare'. This association has been a challenge to successive generations of investigators. Vogt (1926) thought that the exfoliated material blocked the outlets of the angle and so caused glaucoma. He also considered the possibility of pseudoexfoliation being the result of glaucoma. Malling (1938) held that both the capsular changes and glaucoma were secondary to vascular changes in the uvea, whereas Bedell (1926) considered the relationship coincidental, and Trantas (1929) thought that the glaucoma was due to degenerative changes in the excretory channels identical with the change in the lens capsule. Chandler and Grant (1965), and others, pointed to the increased trabecular pigmentation that is often associated with pseudoexfoliation and saw in it a cause of trabecular embarrassment. All these views imply that the glaucoma is secondary and different from chronic simple glaucoma.

Another puzzling fact about this condition is the great variation of its incidence in glaucoma patients in different countries. For example, its incidence among English glaucoma patients is given as 2 per cent while in Norway the figure is 93 per cent (Tarkkanen, 1962). Thomassen (1949), who examined patients in both countries, held that these were true differences. He found an incidence of 79 per cent in Oslo and of 2 per cent in London. If that was so, and the glaucoma is secondary, then, other things being equal, there should be an excess of glaucoma patients in Norway. There are many fallacies in comparing the results of different glaucoma surveys, but the following figures are available.

Bertelsen (1965) found an incidence of glaucoma in Norway of 1·7 per cent in the 50–59 age group and 3·3 per cent in the 60–69 age group. Wright (1966) in Bedford, England, found an incidence of 2·18 per cent in the 50–59 age group and of 2·58 per cent in the 60–69 age group, excluding ocular hypertensives who account for 0·20 per cent in the younger group and 2·44 per cent in the older. More recent investigations have thrown interesting sidelights on the older views as well as opening up new lines of inquiry.

Aasved (1971b) found that the incidence of pseudoexfoliation increases with age and with the severity of glaucoma. Apparently the clinics reporting a high incidence of pseudoexfoliation in Norway have particularly advanced cases referred to them. Aasved (1969) found the incidence of pseudoexfoliation in Birmingham to be of the same order of magnitude as in Norway. Similarly, Jones (1957), in London, found that of glaucoma patients undergoing surgery 5·5 per cent had pseudoexfoliation compared with 2 per cent of

Address for reprints: Redmond Smith, FRCS, Glaucoma Clinic, Moorfields Eye Hospital, City Road, London EC1V 2PD

glaucoma outpatients found by Thomassen (1949).

Aasved (1971c) also noted several interesting facets of the natural history of pseudoexfoliation. It increases intraocular pressure even in the absence of glaucoma. Patients who develop pseudoexfoliation while under observation tend to develop glaucoma at about the same time, so that there is no increase in the incidence of glaucoma with age as there is in patients without pseudoexfoliation (Aasved, 1971a). This is consistent with the findings of Tarkkanen (1962). Moreover, patients with pseudoexfoliation who have glaucoma tend to be younger than those who do not have glaucoma (Aasved, 1971c; Gillies, 1972; Tarkkanen, 1962). This also argues against a progressive onset of glaucoma.

There is evidence to suggest that the manifestations of the syndrome are more widespread than was once thought. Thus Ringvold (1973) found pseudoexfoliated material in the conjunctiva, Vannas (1969) found vascular anomalies in the irides of eyes with pseudoexfoliation, and Laatikainen (1971) found limbal circulatory abnormalities more often in such eyes. Evidence has also been presented against the view that the glaucoma is simply due to trabecular obstruction by pseudoexfoliation flakes or pigment. Tarkkanen (1962) found flakes in the angles of 46 per cent of the non-glaucomatous eyes and in only 50 per cent of the glaucomatous, and while the glaucomatous eyes tended to be more heavily pigmented 65 per cent were graded 1 or 2 on a scale of 4 and, perhaps more significantly, 8 per cent of the non-glaucomatous eyes had grade 3 pigmentation. Tarkkanen further points out that there is a genetic link between pseudoexfoliation and chronic simple glaucoma. Offspring of glaucomatous parents may have pseudoexfoliation and vice versa.

However, it seems that the most telling argument against the simple obstruction view is the fact that quite a number of patients with unilateral pseudoexfoliation have bilateral glaucoma (36 per cent of Tarkkanen's series of 187 patients). The converse is also true. Not all patients with pseudoexfoliation have glaucoma, and it is of interest to know whether non-glaucomatous eyes, either in the presence of pseudoexfoliation or in the other eye, have an increased tendency to glaucoma. This tendency has been assessed on the basis of steroid sensitivity.

Becker and Mills (1963) administered topical corticosteroids to 30 normal volunteers, of whom 40 per cent developed a rise of 6 mm or more in their intraocular pressure, while 90 per cent of 32 glaucoma suspects and 93 per cent of 44 glaucoma patients showed such a rise. (These data are extracted from Becker and Mills's Figs 1 and 7). Armaly (1963) found that 9 (40 per cent) out of 22 normal volunteers over the age of 40 had a rise of intraocular pressure of 5 mm or more under similar conditions. Becker and Hahn (1964) found that after topical corticosteroids 32 per cent of normal volunteers, 92 per cent of glaucoma patients, 80 per cent of glaucoma suspects, and 73 per cent of offspring of glaucoma patients had a rise of 6 mm or more in their intraocular pressure.

We may summarize these results by saying that in a population of normal volunteers about one-third respond to steroids and that this proportion increases to over 90 per cent in chronic simple glaucoma patients, with intermediate values for glaucoma suspects. Gillies (1970) administered topical steroids to 38 non-glaucomatous eyes of 29 patients with pseudoexfoliation. There was a rise in pressure of 5 mm or more in five eyes (13 per cent). Tarkkanen and Horsmanheimo (1966) found that of 33 patients who had bilateral or unilateral non-glaucomatous pseudoexfoliation five (15 per cent) had a rise of 6 mm or more or a reduction in facility of outflow greater than 33 per cent.

It would seem, therefore, that these eyes are no more prone to glaucoma than average eyes, and if anything less so. Furthermore, Pohjola and Horsmanheimo (1971) found that of eyes with pseudoexfoliation that actually had glaucoma only 28 per cent responded to corticosteroids with a pressure rise of 5 mm or more (as against 90 per cent of chronic simple glaucoma eyes), and in all but one of the responders the glaucoma was bilateral.

These authors offer the following explanation. Patients with pseudoexfoliation may have one of two kinds of glaucoma, either primary chronic simple glaucoma, which is bilateral even with unilateral pseudoexfoliation and is steroid responsive, or a secondary glaucoma, which is non-steroid responsive and is confined to the pseudoexfoliated eye. Furthermore, the presence of the pseudoexfoliation gene is strongly contributory to the expression of chronic simple glaucoma, so that steroid-responders with pseudoexfoliation tend to develop manifest glaucoma, leaving only a small proportion of responders among the non-glaucomatous eyes.

Tarkkanen (1962) notes that patients with unilateral pseudoexfoliation and glaucoma, which would be classed by Pohjola and Horsmanheimo as secondary glaucoma, show a high proportion of males, relatively many myopes, a family history of glaucoma, marked pigmentary changes, and a large proportion of high initial intraocular pressures as compared with bilateral cases.

If we now look at Tarkkanen's overall figures with Pohjola and Horsmanheimo's views in mind

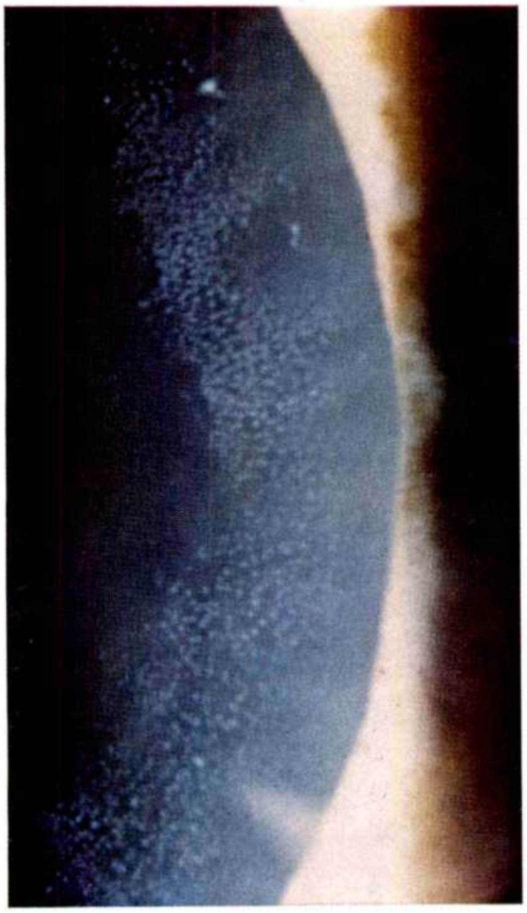

FIG. 1 *Right eye: pseudoexfoliation of lens capsule*

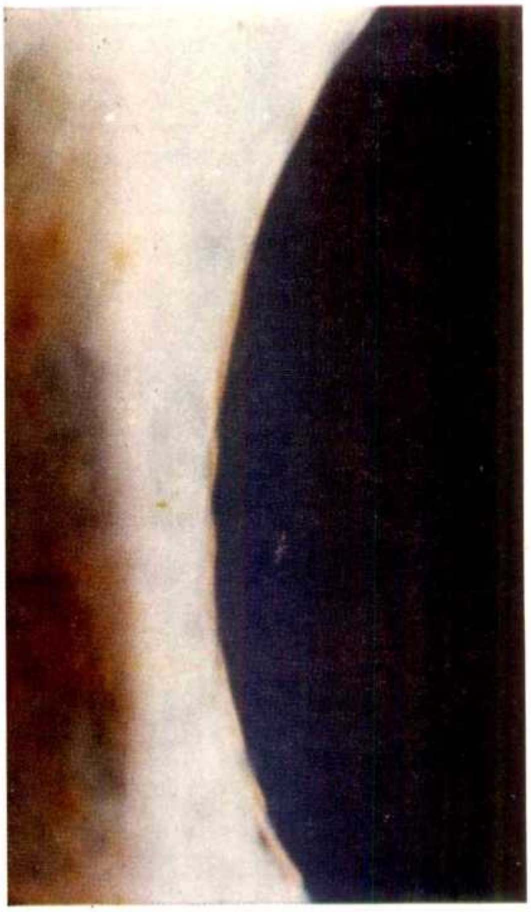

FIG. 2 *Left eye: normal lens capsule*

we see that 60 per cent of all patients with pseudoexfoliation have glaucoma. Of these some have chronic simple glaucoma and some have secondary glaucoma. The relative proportions of these conditions may be estimated from the distribution of glaucoma in patients with unilateral pseudoexfoliation (Table 19). There are 36 per cent of patients with bilateral glaucoma and 23 per cent with unilateral glaucoma. These figures can serve as a measure of the incidence of chronic simple glaucoma and secondary glaucoma respectively.

While the manner in which the secondary glaucoma is produced is not clear the association of chronic simple glaucoma in 37 per cent of cases of pseudoexfoliation also requires explanation. Such an explanation has been put forward by Tarkkanen (1962).

> 'The condition [pseudoexfoliation] may be associated with a gene bearing three characteristics. (1) An abnormality of the drainage mechanism of the aqueous, similar to the one seen in chronic simple glaucoma. (2) Pseudoexfoliation. (3) Pigmentary disturbance. The variations in expression of the gene would explain why the three characteristics are occasionally found together, but sometimes only one or two of them are present.'

The subject of the present report may be viewed as illustrating the thesis of Pohjola and Horsmanheimo.

A search of the English-language literature discovered mention of only five other such cases, where one eye was affected by pseudoexfoliation only and the other by glaucoma only (Trantas, 1929 (two cases); Fahmy, 1936; Wilson, 1953; Good and Ratnaj, 1968). The rarity of this combination seems analogous to the rarity of unilateral chronic simple glaucoma. Leydhecker (1973) states that fewer than 0·1 per cent of cases remain unilateral 10 years after the onset of the disease. Possibly further follow-up would find the glaucoma in these cases becoming bilateral (indeed, Wilson's patient had a pressure of 23 mm in the sound eye). When a little more advanced such bilateral cases would excite no undue interest. They are nevertheless worthy of attention, because they emphasize the fact that pseudoexfoliation and glaucoma, even though closely associated, can arise independently.

We thank Mr Nicholas Brown for the photographs of the anterior segment.

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Senile cataract extraction and diabetes

RITA HILLER AND HAROLD A. KAHN
From the Office of Biometry and Epidemiology, National Eye Institute, Bethesda, Maryland, and Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland

Caird, Hutchinson, and Pirie (1964) and Caird, Pirie, and Ramsell (1969) reported that senile cataract extraction was more common in diabetics than in non-diabetics living in the area of Oxford, England. In the 50–69 age group it was over seven times as common in diabetics as in non-diabetics. Senile cataract in the Oxford study was defined, by exclusion, as all cataracts except those associated with other ocular disease or general disease other than diabetes or attributed to congenital causes.

The object of the study reported here was to determine whether or not similar relationships hold in the United States. To achieve this we used hospital discharge data to estimate US age-race specific odds ratios of senile cataract extractions among diabetics to senile cataract extractions among non-diabetics.

Patients and methods

The Washington Hospital Center (WHC), Washington DC, was selected as a data source because it had a broadly based residency training programme assuring a wide variety of clinical material and also because of its accurate and detailed medical records. For example, for the period January to June 1972 the type of cataract (verified by the physician) was specified in the records on discharge of all but 2·6 per cent of the patients with cataract, while in other hospitals in the area the comparable figure was 30 to 90 per cent. Information on all diagnoses on discharge, age, and race was obtained from WHC for all patients in whom the first listed discharge diagnosis (that is, the condition principally responsible for the patient's hospitalization) was senile cataract extraction, fracture, sprain, or strain during the period from July 1971 to June 1973.

A second data source used was the 1972 Hospital Discharge Survey (HDS) conducted by the National Center for Health Statistics (NCHS), which produced about 225 000 medical abstracts from a stratified random sample of 424 short-stay non-federal hospitals (unpublished data from the 1972 Hospital Discharge Survey, National Center for Health Statistics). The cases taken from this survey were those with a first listed discharge diagnosis of cataract extraction; fracture, sprain or strain; haemorrhoids; and varicose veins (the last two diagnoses were not readily available from WHC). Their classification was by age only, since information on race was not available for many discharges.

WHC and HDS data differed slightly both in diagnosis/operation coding and the number of diagnoses coded per discharge. The HDS records a maximum of five diagnoses and three operations and codes them according to the eighth revision of the *International Classification of Diseases, Adapted for Use in the United States* (ICDA). WHC records a maximum of six diagnoses or operations per discharge and uses the Hospital Adaptation of the *International Classification of Hospital Diseases* (H-ICDA). The diagnosis/operation codes used are shown in Table I.

The third data source used was the 1973 *Household Interview Survey*, National Center for Health Statistics. NCHS prepared, at our request, estimates of age-race specific rates for prevalence of diabetes (unpublished data from the 1973 Household Interview Survey, National Center for Health Statistics). We calculated age-race specific odds ratios to study the relationship of diabetes to the risk of senile cataract extraction. The odds ratio can be most easily understood by first considering the following 2 × 2 table subdividing the present total US population into four groups

		Cataract extraction	
		Present	Absent
Diabetic	Yes	A	B
	No	C	D

where A = No. of diabetics who had cataract surgery.
B = No. of diabetics who did not have cataract surgery.
C = No. of non-diabetics who had cataract surgery.
D = No. of non-diabetics who did not have cataract surgery.
A/B = Relative odds of cataract* to non-cataract among diabetics.
C/D = Relative odds of cataract to non-cataract among non-diabetics.

$\frac{A/B}{C/D}$ is the odds ratio. Clearly, if diabetes raises the risk of cataract the odds ratio will be larger than one.

Address for reprints: R. Hiller, Office of Biometry and Epidemiology, National Eye Institute, National Institutes of Health, Building 31, Room 6A18, Bethesda, Maryland 20014, USA

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*To save clumsy expression we will often use 'cataract' to designate cases of senile cataract extraction and 'non-cataract' to designate cases without extraction. Clearly this paper deals with only a subset of all lenticular opacities.

Table I *Diagnosis/operation codes*

Diagnosis	*Hospital Discharge Survey (ICDA)*	*Washington Hospital Center (H-ICDA)*
Senile cataract in combination with lens extraction	374·9* and 14	374·2 and 12·4–12·6
Fracture, strain, or sprain	800–829 and 840–848	800–829 and 840–848
Haemorrhoids	455	—
Varicose veins of lower extremities	454	—
Diabetes	250	250

*Includes unspecified cataract

An odds ratio of one implies no association between diabetes and cataract and a ratio of less than one implies a negative association. The problem that confronts us is that we do not know the population values A, B, C, and D nor can we directly estimate the ratios A/B and C/D, since the total populations of diabetics and non-diabetics are difficult to sample.

To derive an estimate of the odds ratio we classified samples of cataract cases (from hospital discharges) and non-cataract cases (hospital discharges for each of the controls described above) according to presence or absence of diabetes. The observed frequencies a, b, c, and d are defined as follows:

		First listed discharge diagnosis	
		Cataract	Fracture, etc
Diabetes also listed as discharge diagnosis	yes	a	b
	no	c	d

with $\frac{a/c}{b/d}$ as an estimate of $\frac{A/C}{B/D}$. But since $\frac{A/C}{B/D} = \frac{A/B}{C/D}$, $\frac{a/c}{b/d}$ is also an estimate of the desired odds ratio $\frac{A/B}{C/D}$. This result is very dependent on whether or not our sample data do in fact provide good estimates of the specified population ratios A/C and B/D. This point will be explored further under 'Discussion'. Confidence limits for odds ratios have been calculated according to Cornfield's method as reported by Gart (1971).

Results

As shown in Table II, the WHC odds ratios have very wide confidence intervals at the ages of 40–49 years but at ages 50–69 and 70 and over the confidence intervals are much narrower and the ratios are about 2 and 1 respectively. There is little difference between races. The Hospital Discharge Survey data, which are national in scope, show odds ratios for the relationship of diabetes to the risk of senile cataract extraction of 4·7–7·3, 2·1–3·6, and 0·5–1·1 for ages 40–49, 50–69, and 70 and over respectively. The HDS odds ratios at age 40–49 are well within the previously mentioned wide confidence limits for the WHC odds ratios at this age. The odds ratios for 50–69 and 70 and over are quite similar in both sets of data.

Discussion

Before discussing results we first examine whether we have satisfactory control groups. In a standard diabetes textbook (Marble, White, Bradley, and Kroll, 1971), trauma is mentioned only to conclude that it is not an aetiological factor in diabetes. The absence of any discussion of fractures under the various complications of diabetes suggests that they are not known to be more common in diabetics than in non-diabetics. A National Library of Medicine computer search failed to identify any references relating diabetes to fracture, sprain, or strain during the period January 1970 to August 1974.

Clearly, not all patients with fracture, sprain, or strain are hospitalized, and we need to consider whether those who are represent a biased selection from the viewpoint of presence of diabetes. Because of the increased problems in diabetes management associated with physical stress there probably is a greater tendency to hospitalize for fracture when diabetes is also present than when it is not. We observe that the prevalence of diabetes among WHC patients discharged for fracture, etc., is very close to the estimates of national diabetes prevalence from the Household Interview Survey. The prevalence of diabetes among patients discharged for fracture, etc., in the US Hospital Discharge Survey is somewhat lower than the national prevalence estimates based on household interviews. Thus, although we suspect an upward bias in diabetes prevalence among hospital fracture cases as compared to all fracture cases, which is in the direction of making our estimated odds ratios too low, we do not believe that this bias is very strong.

The use of 'fracture, sprain, or strain' as a control may be criticized because fracture is usually associated with a surgical emergency while cataract is an elective procedure. Thus this control group might not be as suitable as some other selected on the basis of elective surgery. Therefore, we have included two additional control groups, both from the elective surgery category: haemorrhoids and varicose veins of lower extremities.

Table II *Odds ratios for senile cataract extraction: diabetics compared with non-diabetics. Hospital Discharge Survey (ICDA)* 1972 *data by age*. Washington Hospital Center (H-ICDA), July* 1971 *to June* 1973 *data by age and race*

Study population	*First listed discharge diagnosis*	*Age 40–49*				*Age 50–69*				*Age 70+*			
		No. of patients with diabetes also listed		*Odds ratio*	*95 per cent confidence interval*	*No. of patients with diabetes also listed*		*Odds ratio*	*95 per cent confidence interval*	*No. of patients with diabetes also listed*		*Odds ratio*	*95 per cent confidence interval*
		Yes	*No*			*Yes*	*No*			*Yes*	*No*		
HDS (ICDA)	Cataract	7	53	—	—	55	552	—	—	52	813	—	—
(Race not known)	Fractures, etc.	30	1068	4·7	(1·8–11·9)	84	1927	2·3	(1·6–3·3)	102	1712	1·1	(0·7–1·5)
	Haemorrhoids	2	165	—†	(2·0–78·5)	12	251	2·1	(1·1–4·2)	8	67	0·5	(0·2–1·3)
	Varicose veins	6	330	7·3	(2·1–25·6)	11	396	3·6	(1·8–7·4)	5	74	0·9	(0·3–2·8)
WHC (H-ICDA)													
White	Cataract	1	46	—	—	52	480	—	—	45	595	—	—
	Fractures, etc.	2	113	—†	(0·04–17·9)	9	167	2·0	(0·9–4·5)	15	183	0·9	(0·5–1·8)
Non-White	Cataract	6	15	—	—	32	137	—	—	21	144	—	—
	Fractures, etc.	3	110	—†	(2·8–84·7)	13	124	2·2	(1·1–4·7)	6	52	1·3	(0·4–3·7)

*Sample counts adjusted according to sampling weights for each diagnosis within given age group
†Not shown because of small sample size (fewer than 5 cases in one or more cells)

Recognizing that cataract patients will be older than fracture patients, we have tried to adjust for this by reporting age-specific data. For cases in the Hospital Discharge Survey the average age of the cataract cases compared to the average age of the fracture cases is 46·1–44·4, 62·1–59·3, and 77·4–79·8 for the age groups 40–49, 50–69, and 70 and over respectively. The Washington Hospital Center data reflect average ages and age differences almost identical to those shown for the Hospital Discharge Survey. Although these differences exist they are small, and we think any bias resulting from them would be trivial.

Since cataract extraction outside a hospital was rare or non-existent in the US during the period reported, hospital discharges for cataract extraction should represent new additions to the aphakic population rather well. Of course, possibly the persons discharged from a particular hospital after cataract surgery are a biased representation of the cataract surgery cases in the community. They may be, for example, richer or poorer than the total. However, one of the strengths of this study is that the controls are *from the same hospitals* as the cataract surgery cases. Thus, if we have cataract cases that are wealthier than average probably we also have economically privileged controls.

There is a real possibility that the presence of cataract increases the probability of diabetes being diagnosed, assuming that it is present, and vice versa. This bias of ascertainment would tend to increase the estimated odds ratios. In the absence of specific information, we judge this factor as present to only a minor degree.

On the basis of all the above facts we think that our control groups are comparable with the cataract patients in age-specific categories as presented. We should therefore have reasonably good estimates of the relevant population ratios required for our estimates of risk associated with diabetes.

We have used the published Oxford data (Caird and others, 1969) to estimate odds ratios for men and women combined of 7·9 for age 50–69 and 4·3 for age 70 or over. Our data (Table II) show odds ratios of about two and three at age 50–69 and of about one at age 70 or over. Thus, our results clearly show a lesser importance of diabetes as a cataract risk factor at ages over 49 than the Oxford study. This is true whether we compare the Oxford data to the White population from the Washington Hospital Center or to our national data which include non-Whites. In all instances our 95 per cent confidence intervals fail to include the Oxford estimates of risk.

Curiously, our data do not differ greatly from the Oxford data with respect to how common diabetes is among those with cataract extractions, but differ sharply as to the general prevalence of known diabetes (Table III). The Oxford estimates of known diabetes prevalence of 1·2 per cent at ages 50–69 and 1·8 per cent at ages over 70 have been criticized as understating the true prevalence (Ciba Foundation Symposium 19, 1973). If the criticism is valid the Oxford estimates overstate the risk, and they may, in fact, not be essentially different from ours.

Although we found little difference in odds ratios between Whites and non-Whites, diabetes prevalence does differ by race, and readers are cautioned that the data for all races in Table III include only about 13 per cent non-Whites for the US national studies (Current Population Reports, No. 511, 1974) such as Hospital Discharge Survey or Household Interview Survey but 33 per cent non-Whites for Washington Hospital Center.

A study in Copenhagen (Norm, 1967) estimated

Table III *Prevalence (rate per cent) of known diabetes* by age and race*

				Controls				
	Among hospital discharges after senile cataract extraction			*Among hospital discharges after fractures, etc.*			*General survey data*	
	US Hospital Discharge Survey[1]	*Washington Hospital Center*	*Oxford Study*[2]	*US Hospital Discharge Survey*	*Washington Hospital Center*	*Oxford Study*	*US Household Interview Survey*[3]	*Oxford Study (working party)*
Age 50–69								
All races	9·1	12·0	—	4·2	7·0	—	5·6	—
White	—	9·8	11·8	—	5·1	—	5·1	1·2
Non-White	—	18·9	—	—	9·5	—	8·4	—
Age 70+								
All races	6·0	8·2	—	5·6	8·2	—	8·2	—
White	—	7·0	9·7	—	7·6	—	7·9	1·8
Non-White	—	12·7	—	—	10·3	—	10·7	—

*Includes cases diagnosed in hospitals at time of cataract surgery
1 Unpublished data from US Hospital Discharge Survey, National Center for Health Statistics, 1972
2 Caird, F. I., Hutchinson, M., and Pirie, A. (1964)
3 Unpublished data from US Household Interview Survey, National Center for Health Statistics, 1973

a fourfold increase in risk of cataract extraction due to diabetes and a study in Mainz (Marquardt and Kirschbaum, 1971) estimated a tripling of risk. We cannot readily compare these results with ours since the Copenhagen data are not age-adjusted and the Mainz study did not clearly specify the control group used.

Our finding that diabetes may be a strong risk factor for cataract extraction below age 50 is in keeping with a nonquantified statement to this effect in a recent diabetes text (Ellenberg and Rifkin, 1970).

Summary

A study of hospital discharge diagnoses from both national data and data from a local medical centre indicates that diabetes substantially increases the probability of cataract extraction at age 40–49, about doubles or triples the probability for age 50–69, and has little effect on risk at age 70 and over. Strengths and weaknesses of the data are discussed. Other reports, generally estimating a much stronger association between diabetes and probability of cataract extraction, at least at age 50 and above, are critically evaluated.

We thank Mr Lewis Streppa and Mrs Elizabeth Dilts, of Washington Hospital Center, and Mr Abraham Ranofsky, of the Hospital Discharge Survey, NCHS, for making their medical discharge data available. We express our special thanks to Mr Ronald Wilson, of Household Interview Survey, NCHS, for preparing the 1973 summary data on the prevalence rate of diabetes in the US, and to Mr Fred Ederer, Dr Roy C. Milton, Mrs Helen Moorhead, and Mr Frank Mervine for their valuable help on various aspects of this study.

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Pigmented lens striae

GEORGE D. STURROCK AND RAMESH C. TRIPATHI
From Moorfields Eye Hospital and the Department of Pathology,
Institute of Ophthalmology (University of London), Judd Street, London

In his atlas of slit-lamp microscopy of the eye Vogt (1931) described an unusual condition of fine brown radial lines on the anterior lens capsule in the mid-periphery behind the iris. Because pupillary membrane remnants were present in three patients he concluded that the striae represented persistent tunica vasculosa lentis—a view supported by Lugli (1933), Streiff (1935), Bischler (1939), Vogt (1942), and Bellows (1944) when reporting further examples of this condition. Cowan (1961), however, suggested that some cases of 'retroiridic lines' might represent congenital deposition of pigment on zonular fibres. In the absence of any histological study, the precise nature of the pigmented lens striae remained unresolved.

During the past two years one of us (GDS) saw a number of patients with these pigmented lens striae. Since their morphology and distribution seemed inconsistent with a diagnosis of persistent tunica vasculosa lentis we examined three of the lenses by electron microscopy. This paper correlates for the first time the clinical with the ultrastructural features of pigmented lens striae.

Patients and methods

Pigmented striae on the anterior lens capsule were seen in six women and one man aged between 51 and 87 years. Two of the patients had chronic glaucoma, one had a retinal hole, and four were in hospital for cataract surgery. The lenses from three of the patients with cataracts were processed for examination by electron microscopy.

In the first patient chymotrypsin was used to dissolve the zonule before removal of the lens. The lenses of the other two patients were extracted without the use of this enzyme. The lens in one case was delivered with capsule forceps, taking care to grasp the capsule some distance away from the previously determined position of the pigmented striae. In the third patient the lens was removed with a cryoprobe, purposely freezing on to the capsule at the site where striae had been noted preoperatively.

The extracted lenses were fixed immediately in isotonic buffered glutaraldehyde (2·5 per cent solution). The pigmented striae were identified under a dissecting microscope, tissue blocks were postfixed in 1 per cent buffered osmium tetroxide solution and, after dehydration, were finally embedded in Araldite. Using glass knives, sections were cut on an LKB Ultratome III at about right-angles to the long axis of the striae. Thin sections were stained with uranyl acetate and lead citrate and micrographs were taken with a JOEL 100C electron microscope.

Results

In all seven patients the pigmented striae could be seen only when the pupil was dilated. They were situated on the anterior lens capsule in the mid-periphery, predominantly on the nasal side (Fig. 1). Although arranged in a basically radial manner, some striae forked at an acute angle (Fig. 2). The number of striae visible varied from only three or four in some patients to several dozen in others. Individual striae appeared as very fine straight lines of uniform width a millimetre or more in length. In two patients with pigment speckling of the anterior lens capsule some striae had a beaded appearance due to small deposits of pigmented particles. Most striae were dark brown in colour in focal illumination, although in one patient fine translucent grey striae were also visible.

The three extracted lenses were examined under a dissecting microscope. No striae could be found on the lens which was extracted after irrigation of the posterior chamber with chymotrypsin. Striae were seen, however, on the two lenses removed without the use of chymotrypsin (Fig. 3).

Analysis by electron microscopy showed that the pigmented striae consisted of variable-sized, electron-dense, round or oval granules entrapped in bundles of fine fibrils. Sections along the length of the striae showed that near their termination the fibrillar bundles were in close contact with the lens capsule (Fig. 4) whereas peripherally they were separated from the surface of the lens capsule (Fig. 5). The fibrillar bundles were composed of numerous fine filamentous structures cut transversely or obliquely; the individual fibrils varied from 12–15 nm in diameter and had a faint axial

Address for reprints: Dr R. C. Tripathi, Institute of Ophthalmology, Judd Street, London WC1H 9QS

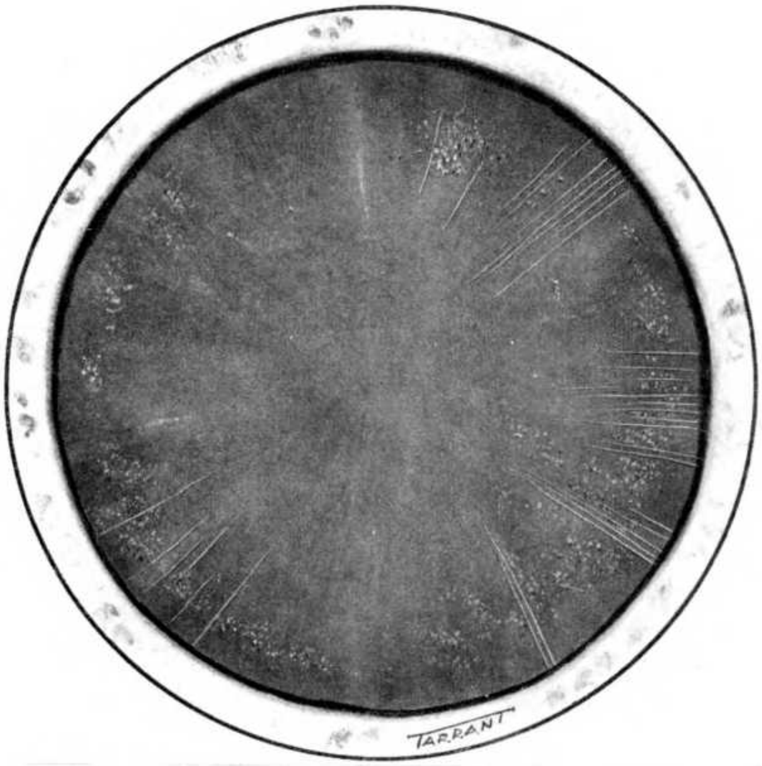

FIG. 1 *Painting to show radial disposition of pigmented striae on mid-periphery of anterior lens capsule. Pigment speckling also visible in same region. Right eye of woman aged 70 with chronic simple glaucoma and shallow anterior chamber*

periodicity of 20–25 nm (Fig. 6). The electron-dense pigment granules were irregularly dispersed along the fibrillar bundles, and at higher magnification appeared to consist of finely particulate or amorphous material and occasional granules showed fibrillar profiles (Fig. 6). No cell organelles were seen in relation to these granules.

Discussion

A review of the 70 reported cases of pigmented lens striae shows that they occurred most often in middle-aged and elderly patients, of whom 80 per cent were women. Except for a girl aged 17 (Vogt, 1942) and a young man of 27 (Bellows, 1944), the 70 patients were aged between 40 and 87 years. The striae were bilateral in over half the cases, although more pronounced in one eye. Most authors have commented on the predominantly nasal disposition of the striae, which remains unexplained.

The older-age incidence of pigmented lens striae strongly suggests that the pigmentation is acquired, the most likely source being the pigment layer of the iris. In support of this is the observation that when the pupil can be dilated sufficiently pigmented lines are often seen to terminate before reaching the extreme periphery of the lens, which, owing to its backward curvature, is not usually in contact with the iris. Examination of the lens in four patients with congenital aniridia showed no sign of pigmented lens striae (Iwaszkiewicz-Bilikiewiczowa and Janukowiczowa, 1969).

In many of the reported cases of pigmented lens striae there was evidence of generalized pigment dispersion in the anterior segment. Lugli (1933) mentioned pigment deposition on Descemet's membrane in a patient with iris atrophy and pigmented lens striae, and Bischler (1939) described pseudoexfoliation (commonly associated with pigment dispersion) in one patient with pigmented lens striae and a Krukenberg spindle in a second patient. Stankovic and Stankovic (1962) noted much pigmentation of the trabecular meshwork and raised intraocular pressure (without field loss) in nine out of 14 patients with pigmented lens striae, none of whom had pseudoexfoliation or a Krukenberg spindle.

The illustrations of Vogt (1931) of pigmented lens striae also show non-pigmented, greyish translucent striae in some of his patients. Similar non-pigmented striae were described by Lugli (1933), Bischler (1939), Bellows (1944), and Berliner (1949) in patients with pigmented lens striae, and they were also seen in one of the seven patients presented here. These grey striae resemble the condition called *Strahlenkranztrübung* originally described in glass-workers by Schläpfer (1930) and Vogt (1931). Subsequently Abramowicz (1933) and Bücklers (1939) found the same condition in a high proportion (90 per cent and 72 per cent respectively) of patients not engaged in glassmaking or foundry work.

The grey striae of *Strahlenkranztrübung* are not visible in the zone of specular reflection from the anterior surface of the lens, and were therefore assumed to be subcapsular by Vogt (1931), Abramowicz (1933), and Bücklers (1939), who did not relate them to pigmented lens striae. Abramowicz (1933), however, found pigmented lens striae associated with grey striae in one patient and in another noted that an incomplete ring of grey striae, concentric with the pupil, was interrupted only at the site of an iridectomy performed 13 years previously for glaucoma. Bischler (1939) recorded the almost total disappearance of bilateral lens striae, some grey-blue and some pigmented, after bilateral iridencleisis procedures performed in a woman of 66. In both of these patients intraocular surgery may have disturbed their lens striae, suggesting that the non-pigmented striae were, like the pigmented lens striae, situated on the surface of the capsule. Bischler also described the spontaneous disappearance of well-marked pigmented lens striae 15 months after they were first observed in a woman of 45 who presented with presbyopia. Possibly, therefore, the grey striae of *Strahlenkranztrübung* are similar in nature to the non-pigmented striae sometimes associated with pigmented lens striae.

Electron microscopical analysis clearly shows that pigmented lens striae are formed by pigment granules trapped within the fibrillar bundles of the zonules. The absence of any other cellular components associated with the pigment granules suggests that they entered the zonular bundles as free-floating pigment and were probably not deposited by wandering cells or elaborated locally. The morphological appearance of the granules seems consistent with an origin from the uveal tract, the pigment layer of the iris being the most likely source (Feeney, Grieshaber, and Hogan, 1965).

Pigmented lens striae can be differentiated clinically from conditions such as 'persistent pupillary membrane', posterior synechiae showing as pigmented streaks after mydriasis, and pseudoexfoliation associated with pigment dispersion. The mesodermal strands of a 'persistent pupillary membrane' are much coarser than pigmented lens striae and rarely have a strictly radial orientation. The strands, which may be multiple to form a net-like pattern, are almost invariably attached to the iris collarette. Mydriasis commonly alters the disposition of pupillary strands since they are usually distensible and stretch with the pupil. Pupillary strands may coexist with pigmented

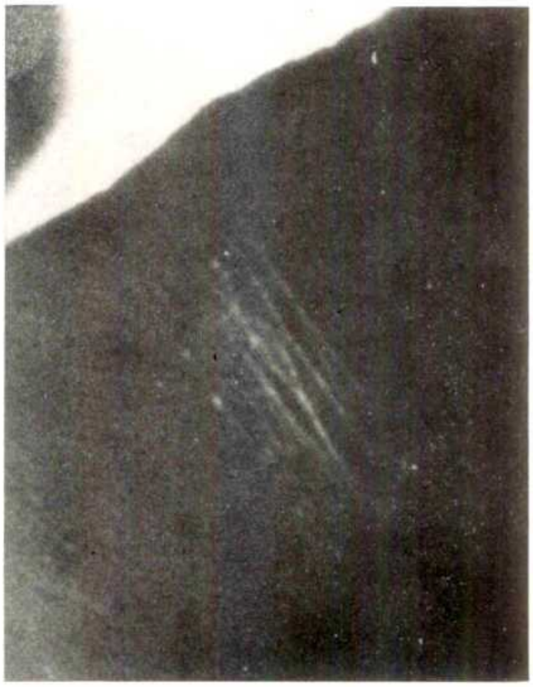

FIG. 2 *Slit-lamp photograph of pigmented lens striae near margin of dilated pupil (white zone). Note acute forking of some striae. Left eye with retinal hole of man aged* 66. (≈ × 80)

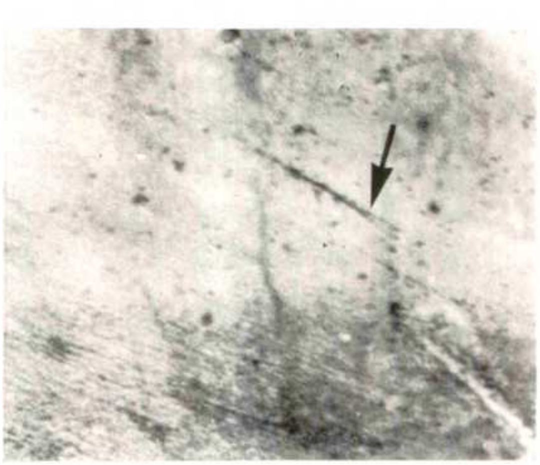

FIG. 3 *Macrophotograph of extracted lens showing pigmented stria which forks (arrow) at insertion into anterior lens capsule. Epithelial cells and lens fibres visible in the background.* (≈ × 70)

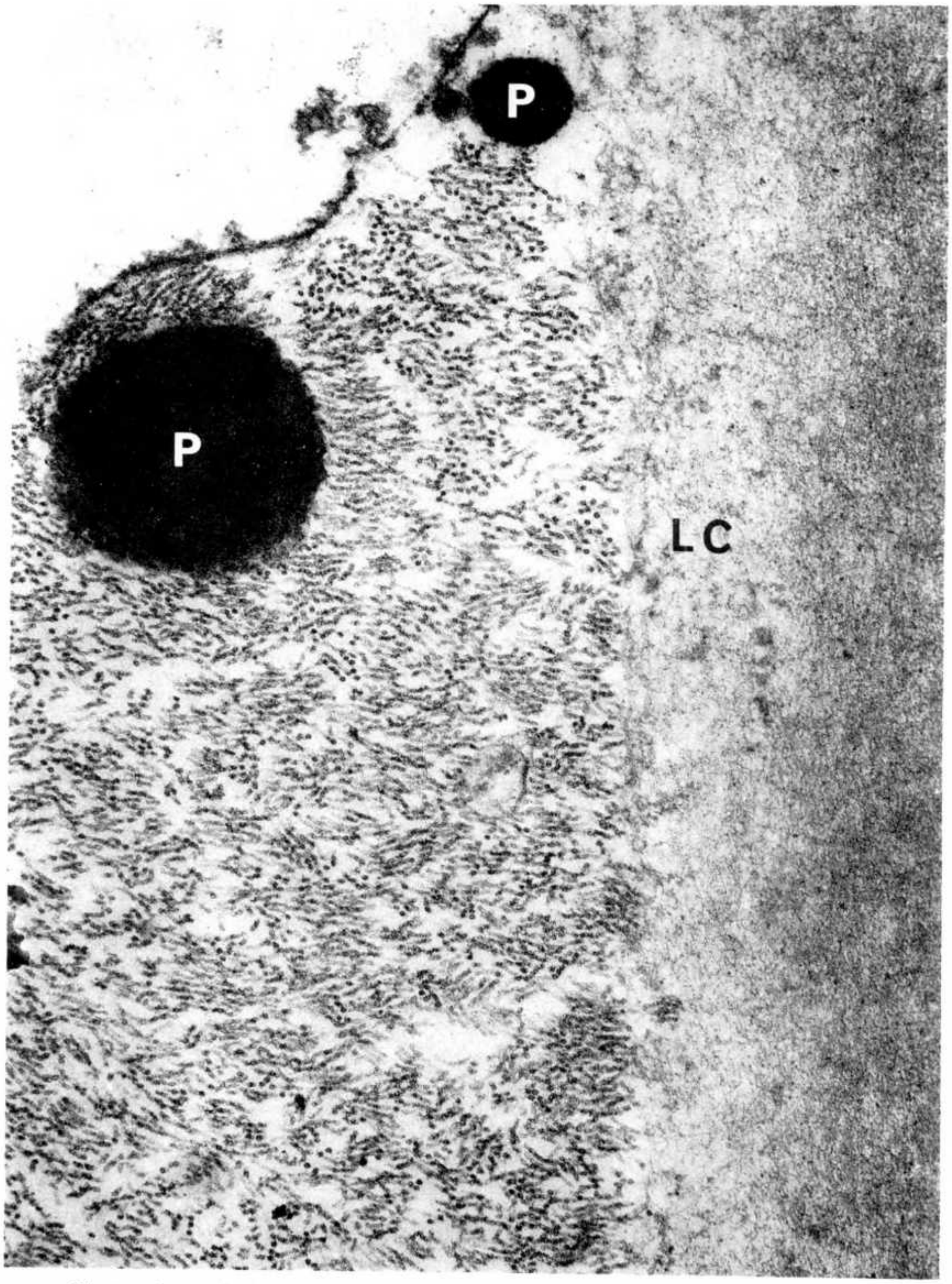

FIG. 4 *Electron micrograph of pigmented lens stria in section near attachment to lens capsule (LC). Stria consists of fine fibrils (cut transversely and obliquely) with characteristics of fibrils of zonular bundles. P = trapped pigment granules. (Fixed GA/OsO_4, stained UA/LC.* × 60 000)

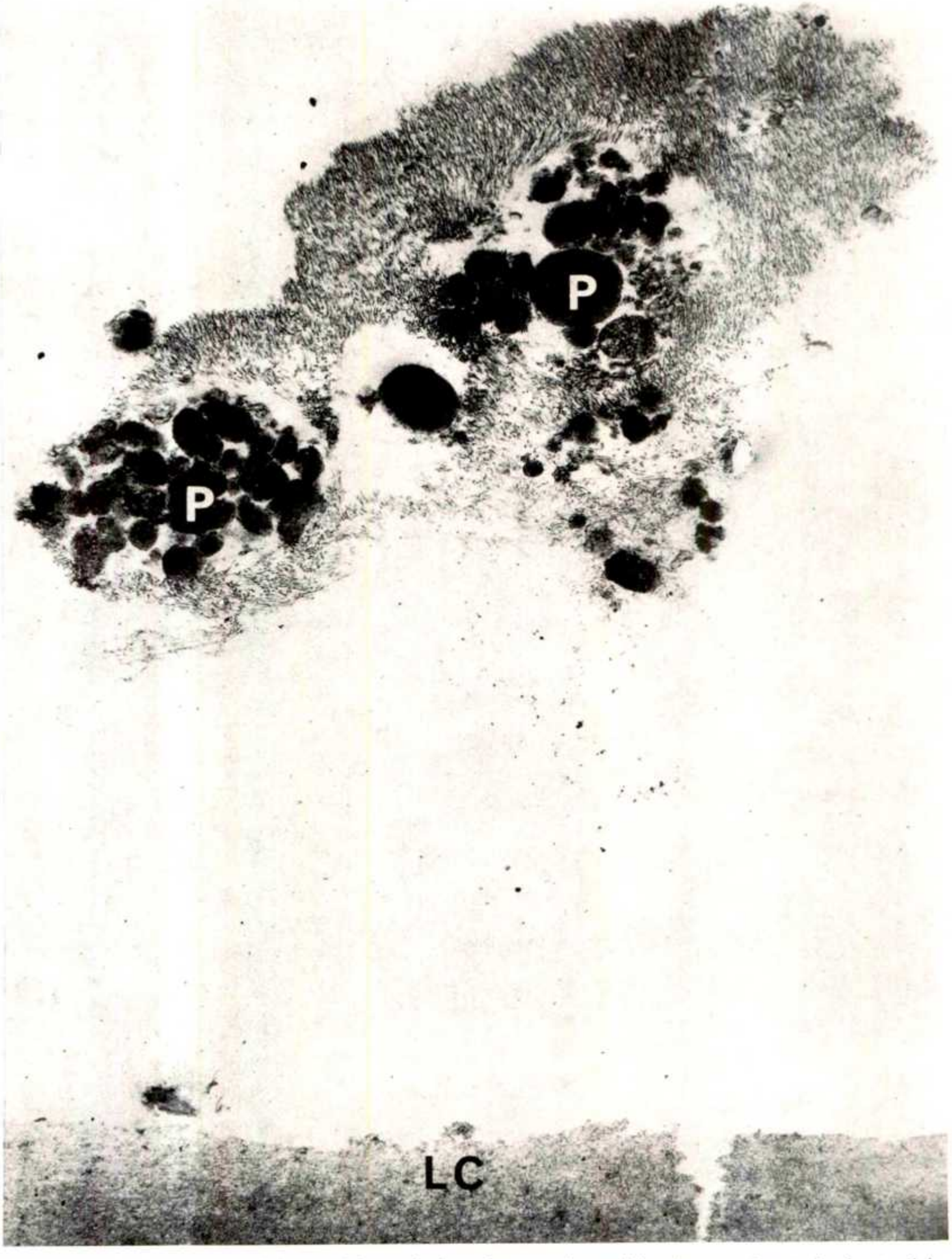

FIG. 5 *Electron micrograph of pigmented lens stria in section at region peripheral to attachment showing spatial relationship of stria with lens capsule (LC). Note numerous pigment granules (P) entrapped by the fibrillar component of the stria. (Fixed GA/OsO4, stained UA/LC. × 22 800)*

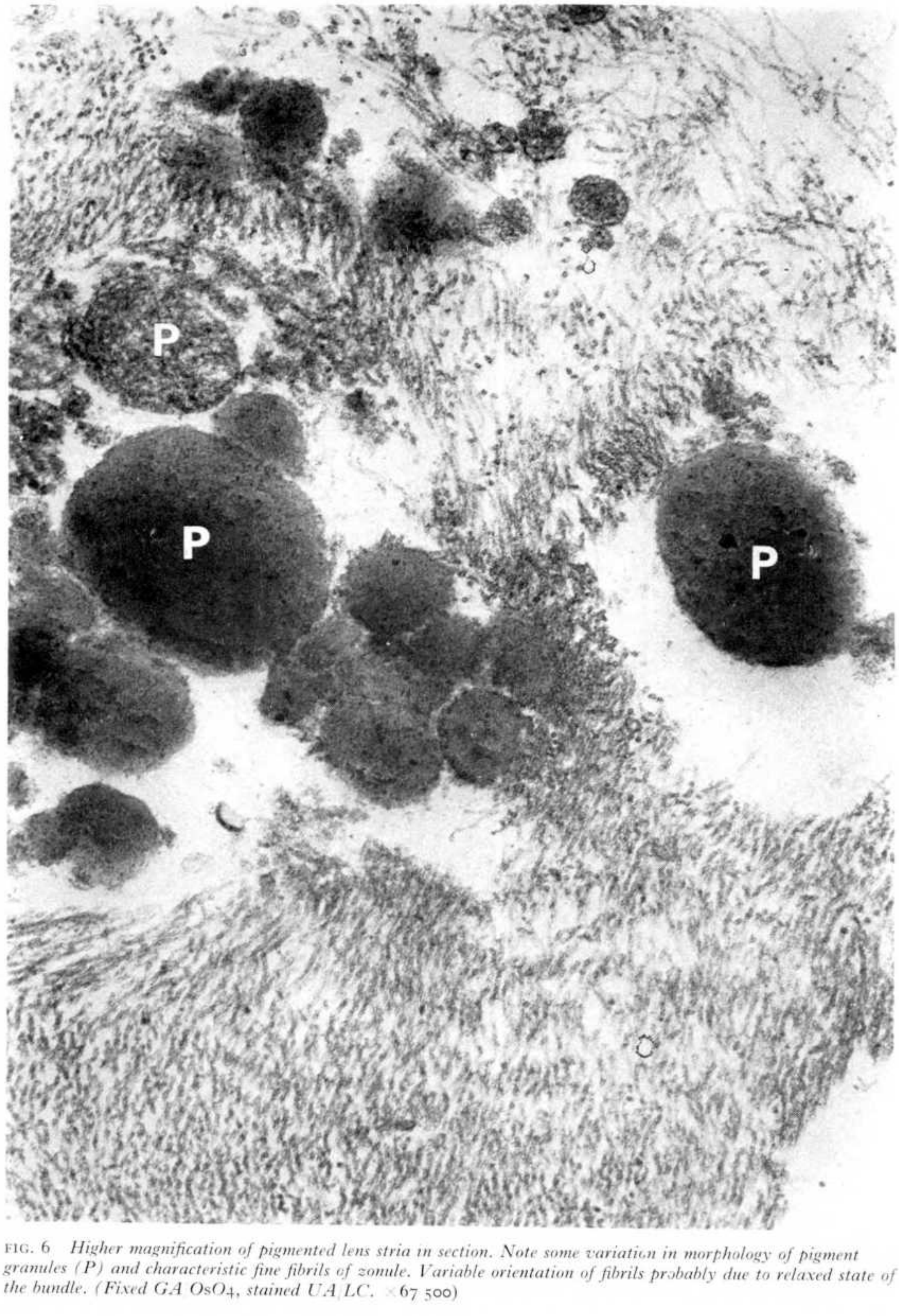

FIG. 6 *Higher magnification of pigmented lens stria in section. Note some variation in morphology of pigment granules (P) and characteristic fine fibrils of zonule. Variable orientation of fibrils probably due to relaxed state of the bundle. (Fixed GA/OsO_4, stained UA/LC.* ×67 500)

lens striae as in three of Vogt's cases (Vogt, 1931).

The pigmented streaks of posterior synechiae are situated more centrally on the lens than pigmented lens striae and are attached to the pupil margin. They are also much broader than striae and their postinflammatory origin is usually evident.

The diagnosis of pseudoexfoliation is suggested by the presence of blue-grey floccules on the pupil margin and confirmed by dilating the pupil to reveal the characteristic peeling sheets of pseudoexfoliative material on the lens surface with an annular clear zone corresponding to the resting position of the pupil. Pseudoexfoliation may also coexist with pigmented lens striae (Bischler, 1939). Ultrastructurally there is little doubt that the fine fibrillar bundles analysed in specimens belong to the zonular system (Hogan, Alvarado, and Weddel, 1971; Raviola, 1971; Takei and Ozanics, 1975), and they could be differentiated from the coarse and haphazardly arranged collagenous fibrils of pupillary membranes (Matsuo and Smelser, 1971). Pigmentation of zonular fibres on the anterior lens capsule renders them visible with the biomicroscope and also shows that some fibres are inserted more centrally on the anterior lens capsule than is commonly described (Duke-Elder, 1961).

Summary

The clinical features of pigmented lens striae were studied biomicroscopically in seven patients. The lenses of three of these, obtained by cataract surgery, were examined by electron microscopy to determine the structure of the striae. We concluded that the striae are not formed by remnants of tunica vasculosa lentis, as earlier workers believed, but consist of fine fibrils of zonular bundles entrapping pigment granules of uveal origin.

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Familial syndrome of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (didmoad) in childhood

S. F. J. PILLEY* AND H. STANLEY THOMPSON
From the Department of Ophthalmology, University Hospitals and Clinic, University of Iowa, Iowa City

Marquardt and Loriaux (1974) describe a kinship of two siblings with the combination of diabetes mellitus, diabetes insipidus, and optic atrophy in which there was additional evidence of renal tract dilatation, amino-aciduria, and neurosensory hearing deficit. These authors cite 41 cases of optic atrophy and diabetes mellitus reported since an association of these conditions was first described by Wolfram (1938). Damaske, Cohen, Gutman, and Schumacher (1975) reassess these and three more cases to review a full syndrome of diabetes mellitus, diabetes insipidus, and optic atrophy. A total of 22 cases of the full syndrome are presented in these two publications.

Combining the information in these two publications the full syndrome consists of diabetes mellitus, diabetes insipidus, optic atrophy, neurosensory deafness, urinary tract abnormalities (such as hydroureter and neurogenic bladder, probably secondary to diabetes insipidus), and amino-aciduria. Several cases have also had retinal pigmentary disturbance, ataxia, gynaecomastia, intermittent or complete amenorrhoea, hypoandrogenicity, and episodic seizures.

The onset of diabetes mellitus in all of these cases was in infancy or youth. Often two or more siblings were affected but no other members of the family were involved, save occasionally for a history of diabetes mellitus in the family. The sexes were equally affected (Damaske and others, 1975), and although diabetes mellitus usually preceded both diabetes insipidus and optic atrophy this was not always so. The diabetes insipidus often remained undiagnosed until the children continued to have polyuria despite effective therapy for their diabetes mellitus. The severity of each of the three major findings (diabetes mellitus, diabetes insipidus, and optic atrophy) varied, although diabetes mellitus seems to be a constant finding (Sunder, Danowski, Kenny, Khurana, Sun, Nolan, and Stephan, 1972). The other findings in these patients such as neurosensory deafness, urinary tract abnormalities, and amino-aciduria were also highly variable, but may have been missed in earlier cases (Tunbridge and Paley, 1956).

No patients with this syndrome have come to necropsy, although two have undergone craniotomy. In these (Sunder and others, 1972; DeLawter, 1949) the only abnormal findings were arachnoïditis in the region of the optic chiasm. Single cases of the syndrome have occurred at the age of 14 after head trauma (Chute, Rebham, Bain, and Kruyff, 1962), with haemorrhagic softening of the hypothalmus (Chute and others, 1962), and after a prolonged febrile illness of unknown origin (Rose, Fraser, Friedmann, and Kohner, 1966). One case has been reported of a patient with Laurence-Moon-Biedl syndrome who also had diabetes mellitus, diabetes insipidus, and optic atrophy in addition to retinitis pigmentosa (Faccaro and Gastaldi, 1952).

The combination of diabetes mellitus, diabetes insipidus, and other less common pituitary abnormalities strongly suggests that the causative lesion is in the region of the hypothalmus, but the pathogenesis remains a mystery. The frequent involvement of siblings is strong evidence for a genetic origin, although there is only one report of the condition affecting more than one generation (Shaw and Duncan, 1958). The mode of the inheritance, if it is indeed a single genetic abnormality, would be most consistent with an autosomal recessive gene (Rose and others, 1966; Sunder and others, 1972; Bretz, Baghdassarian, Graber, Zacherle, Norum, and Blizzard, 1970).

For convenience we refer to this condition as the DIDMOAD syndrome, from the initial letters of the component disorders: Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness. We report two siblings with the syndrome. They are the 23rd and 24th reported cases of the primary triad.

Case reports

CASE 1

A boy aged 13 was referred to the University Hospital, Iowa City, in March 1974 with a history of recurrent enuresis, which had begun about 1½ years before,

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Address for reprints: S. F. J. Pilley, FRCS, National Hospital for Nervous Diseases, Maida Vale, London W9

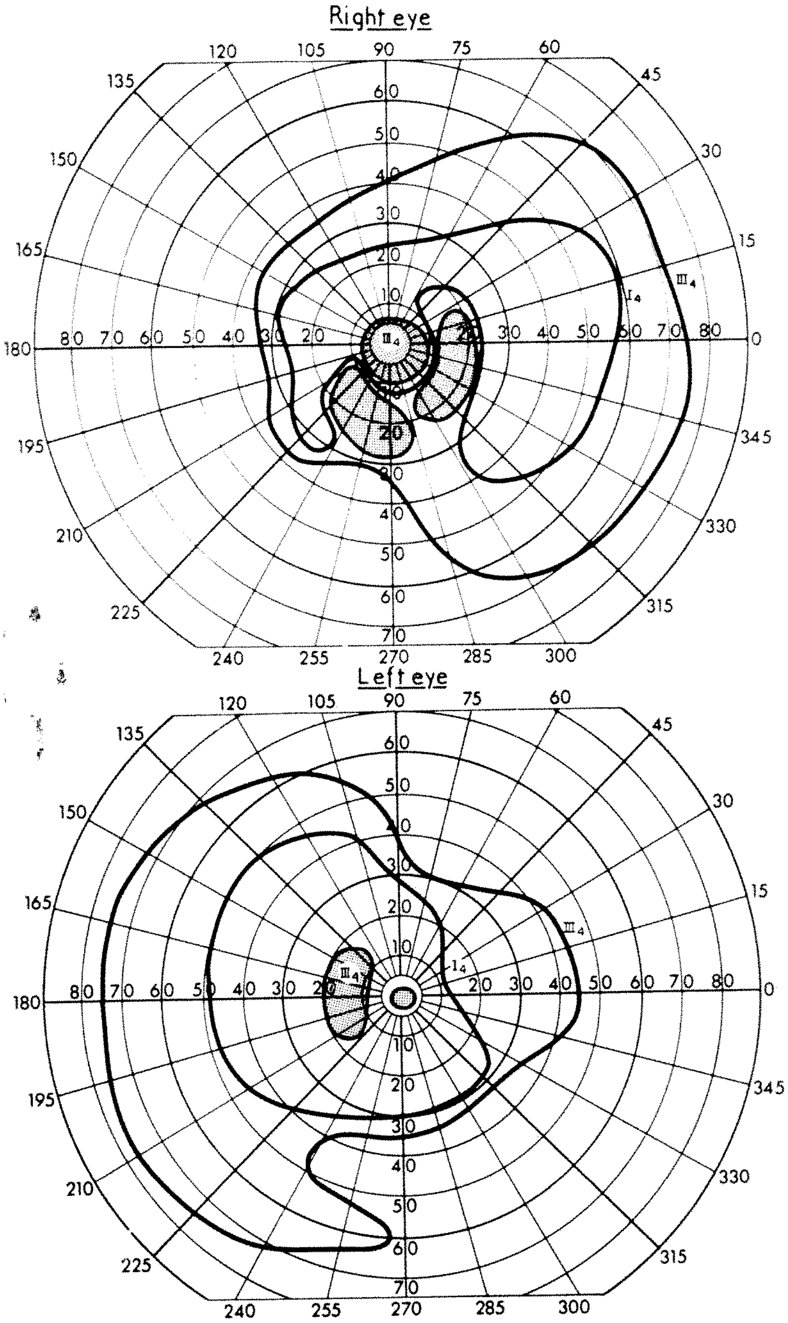

FIG. 1 *Visual fields in Case 1, 18 July 1974*

some difficulty in initiating micturition, and some hesitancy. There were no other urinary symptoms of recent onset, although there was a long history of frequency of micturition (about every two hours) and a high daily fluid intake. Past medical history was uneventful save for gradually deteriorating visual acuity over about the preceding two years. The patient had had visual acuities of 20/20 in each eye when at kindergarten, but two years later, in 1969, they had deteriorated to 20/60 in each eye. There was also some 'minor disc pallor'. In 1972 the acuity was about 20/100 in each eye. An intravenous pyelogram before referral had shown severe hydronephrosis and a large bladder, and a micturating cystogram had shown much reduced bladder function.

On admission to the University Hospital the urinary

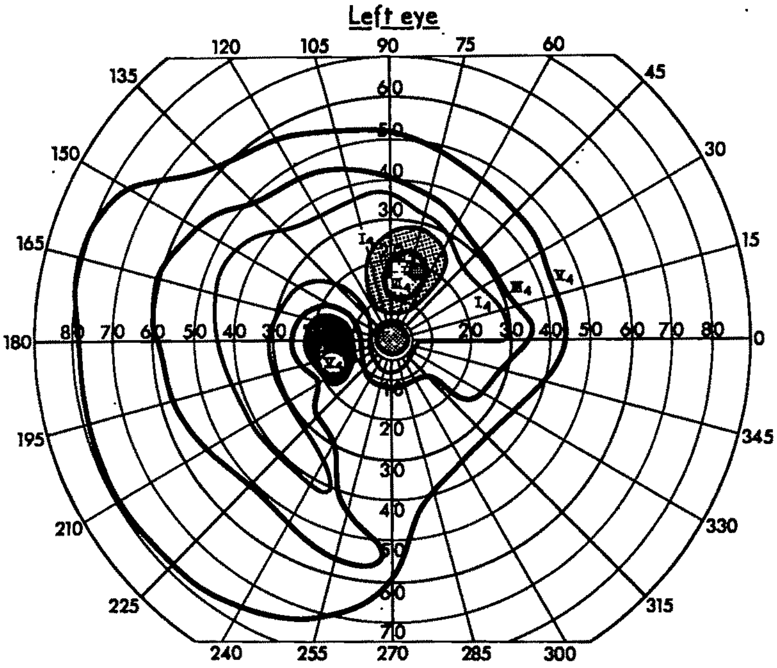

FIG. 2 *Visual field in Case 1, 19 June 1975*

findings were confirmed, and on cystourethroscopy a valve-like obstruction was seen in the region of the veru montana. Urine volumes appeared to be unusually large and urinary specific gravities unusually low. Daily urine output was about 11 litres. The child was referred for consideration of diabetes insipidus. A water deprivation test was strongly positive, with 9 hours of water deprivation resulting in an increase in urinary specific gravity from 1001 to only 1004 and a loss of body weight of 2 kg. A pitressin stimulation test showed a rise in urinary specific gravity to 1022 and a maximum urine osmolality of 454 mOsm. In view of the recent onset of diabetes insipidus in association with bilateral optic atrophy a full neurological investigation was done to exclude mass lesions in the region of the sella turcica. Clinical examination was normal save for bilateral optic atrophy. Skull and chest radiographs were interpreted as normal, as also were brain scan, spinal fluid examination, EEG, optic foraminae radiographs, and EMI scan. A right carotid angiogram was normal save for slight upward tilt of the anterior cerebral artery, which was of doubtful significance. Pneumoencephalography was interpreted as normal. A random blood sugar investigation was reported as abnormal, and a glucose tolerance test showed evidence of clinical diabetes mellitus. Treatment was begun with diet and insulin, although insulin was later discontinued.

Visual acuities were 20/200 in each eye for distance, improving to 20/100 in each eye for near, and to 20/70 when tested binocularly for near. Anterior segment examination was completely normal, as were ocular motility, intraocular pressure, and pupillary examination (although later pupillography showed minor reduction in the pupillary light reaction and increase in the latency of this reaction). There was bilateral optic atrophy and minimal pigment mottling at both maculae. Visual fields showed bilateral dense central scotomata and arcuate type defects (Fig. 1). There was a dense achromatopsia consistent with the degree of visual acuity and visual field loss. Fluorescein angiography was normal. Serum cortisol levels were reduced at 13·1 (8 am) and 8·8 μg/100 ml (10 am), the normal range for this laboratory being 10–22 μg/100 ml for morning specimens. T_3, T_4, and T_3 radioimmunoassay were all normal. Serum biochemical values and haematology scan were unremarkable save for raised blood sugar. Audiography showed no hearing loss.

The patient was discharged with a diagnosis of (*a*) pitressin-sensitive diabetes insipidus; (*b*) chemical diabetes mellitus; (*c*) bilateral optic atrophy; and (*d*) bilateral hydroureter and bladder dysfunction, probably secondary to diabetes insipidus.

Treatment at that time consisted of pitressin injections, urocholine, and urinary antibiotic. This treatment remained essentially unchanged until May 1975, when the diabetes mellitus had become more apparent with blood sugars in the region of 335–411 mg/100 ml. Oral hypoglycaemic therapy was inadequate and insulin treatment was begun. Regular ophthalmological review showed no change in visual acuity, motility, or appearance of the anterior or posterior segment, but there was some evidence of further left visual field loss at the last review in June 1975 (Figs 1 and 2).

CASE 2

A 16-year-old girl, sister of the patient in Case 1, was first examined at University Hospital in July 1974. There was a long history of high daily fluid intake and polyuria, but otherwise the medical history was normal

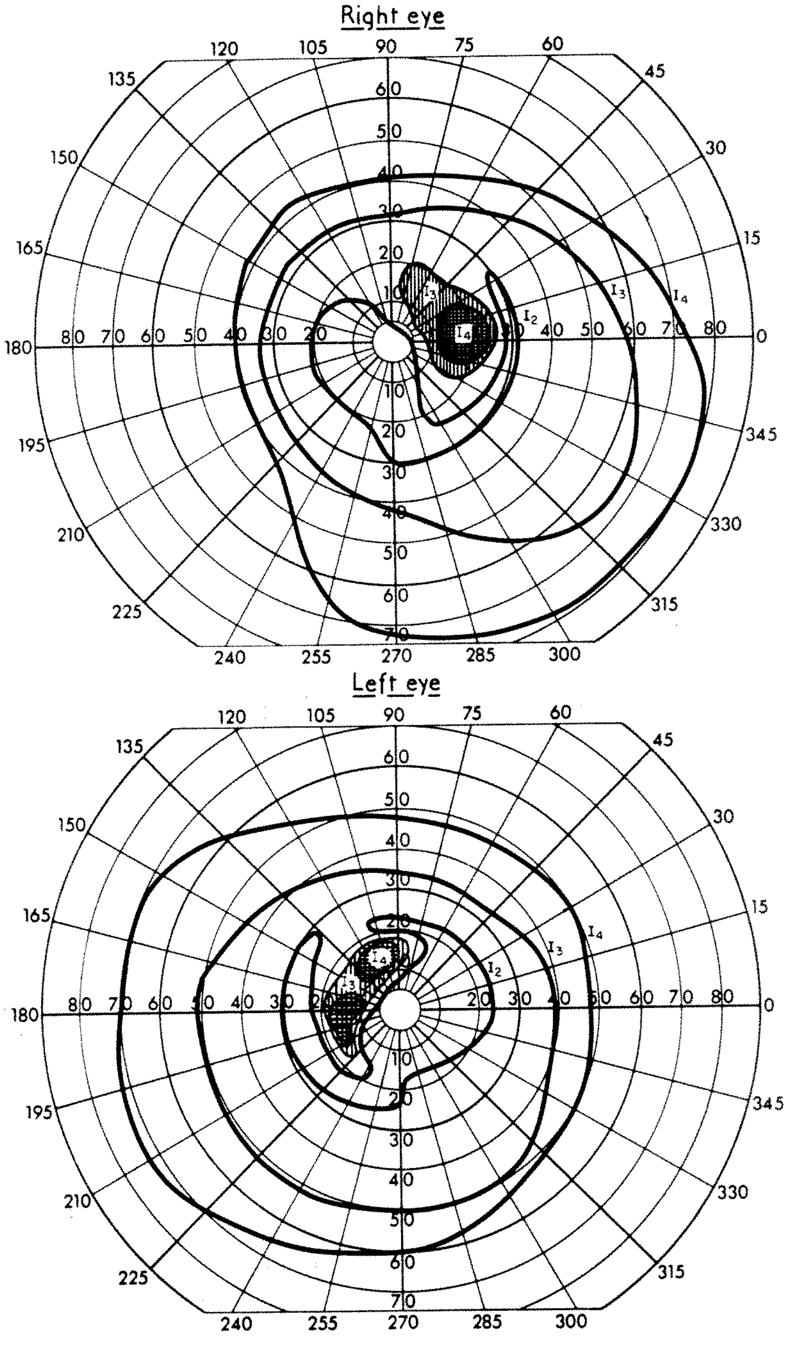

FIG. 3 *Visual fields in Case 2, 17 July* 1974

up to the age of 12 years. At that time a diagnosis of diabetes mellitus had been made and treatment begun with insulin. Despite treatment high fluid intake and polyuria persisted and resulted in her referral to us after we had seen her brother for similar symptoms.

The patient's height and weight were normal for her age, and there was no abnormality on general clinical examination save for bilaterally pale optic discs and glycosuria. Haematological and biochemical investigations were normal except for a raised random blood sugar of 218 mg/100 ml. Chest and skull radiographs were normal. T_4 was normal (7·7 µg/100 ml) and there was no evidence of growth hormone or gonadotrophin deficiency. An intravenous pyelogram showed bilateral hydronephrosis with good renal function, and a cystometrogram showed a dilated bladder with residual urine. Urine specific gravities throughout her stay in hospital remained in the region of 1·013 or less. The results of a water deprivation test were equivocal and though the patient probably had diabetes insipidus the condition was mild and certainly did not require pitressin therapy.

The visual acuities were 20/70 right eye and 20/50 left eye with maximum correction. Anterior segment examination was normal, as were ocular motility, intraocular pressure, and pupillary examination. Fundoscopy showed bilateral, though minor, optic atrophy, especially at the temporal margin of the discs. The visual fields showed bilateral arcuate defects of fairly minor degree (Fig. 3). Colour vision and fluorescein angiography were normal. The patient was discharged with a diagnosis of (*a*) clinical diabetes mellitus, (*b*) bilateral optic atrophy, (*c*) bilateral hydronephrosis and dilated bladder with residual urine, and (*d*) possible borderline diabetes insipidus.

Treatment at this time was insulin and urocholine. On follow-up there was no real alteration in symptoms or signs and, in particular, there was no change in ophthalmic findings and no apparent progression of visual field or acuity deficits. An audiogram was normal save for some loss in the higher frequency range (Fig. 4).

FAMILY HISTORY

Both these children were the result of normal pregnancies and, apart from the usual childhood diseases, they had suffered no serious illnesses. Diet for the affected cases, as for the entire family, was normal and complete, and there was no history in either case of any significant previous trauma. The affected children were two of four siblings. After full ocular examination of both the unaffected siblings, both parents, and all of the parents' siblings, including visual acuity, Goldmann visual field, and fundus examination, there was no evidence that any other member of the family was visually affected (Fig. 5).

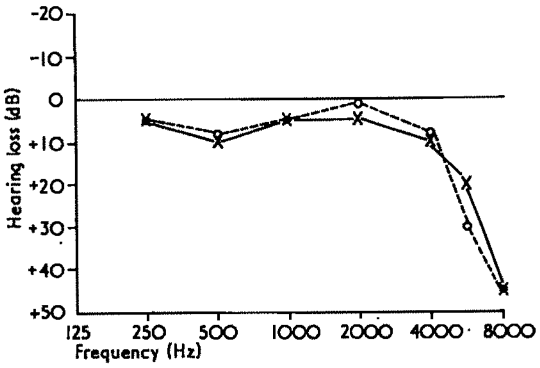

FIG. 4 *Audiogram in Case 2, 16 June 1975*

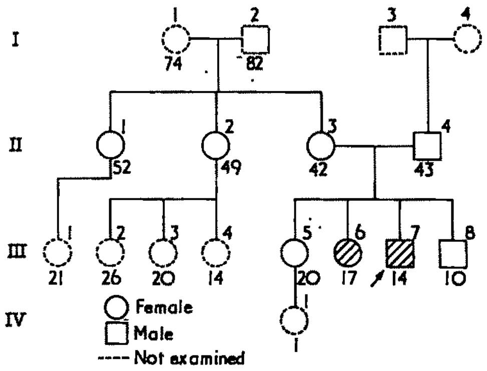

FIG. 5 *Family tree*

Conclusion

A hereditary syndrome probably exists consisting of (*a*) diabetes insipidus, (*b*) diabetes mellitus, (*c*) optic atrophy, and (*d*) deafness. The severity of each of the parts of this syndrome is variable, and different patients, even within the same kinship, show differing clinical patterns. The primary triad, however, is present often enough for it to be advisable to make a careful search for the full spectrum of abnormalities in children (and their siblings) presenting with diabetes mellitus and optic atrophy. The pathogenesis of the syndrome is unknown, but it may be that it is familial, and if genetic, the inheritance is most probably autosomal recessive.

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Immunoglobulins in endogenous uveitis

M. S. NORN
From the Ophthalmological Department, Kommunehospitalet, Copenhagen

Plasma electrophoresis gives information on the albumin and globulins in the blood. Globulin is divisible into α_1, α_2, β_1, β_2, and γ globulin. Gamma globulin is immunoglobulin, which again is divisible into immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM).

Goodner (1968) found that the gamma globulin level was often raised in anterior uveitis, but that it was often lowered in posterior uveitis.

Aronson (1968) showed that IgM levels could be raised in uveitis. Among 37 patients with acute unilateral iridocyclitis he found that 34 had raised levels of IgM and 17 lowered levels of IgG. The method used, however, was simple qualitative serum electrophoresis.

Raised IgM represents a genetically-determined tendency towards rheumatic reaction (Aronson, Elliott, Moore, and O'Day, 1970). Aronson even suggested that some individuals (those who had had raised levels of IgM since birth) were liable to get endogenous uveitis, but not herpes, while those with lowered levels of IgA might become affected with herpes, but not uveitis.

Vasinca (1971) likewise found that the gamma globulin level was raised in uveitis, while the albumin level was found to be lowered, but significant values were found only in acute iritis.

Koliopoulus, Perkins, and Seitanides (1970) found levels of IgM were raised in four cases of uveitis, but not in 13 cases of retinal vasculitis without uveitis. The method employed was that of radial immunodiffusion.

Ghose, Quigley, Landigan, and Asif (1974), on the other hand, likewise using the radial immunodiffusion technique, found normal immunoglobulin values in serum from five patients with uveitis.

The object of the present study was to estimate the immunoglobulin values in different forms of uveitis by the most accurate quantitative method.

Material and method

The clinical series comprised all patients with endogenous uveitis (a total of 300) referred to the Ophthalmic Outpatient Department, Kommunehospitalet, during the period 1968 to 1974.

The age incidence is shown in the Figure. The average age was 46·8 years, and 58 per cent of the patients were men. The types of uveitis are shown in Table I.

Blood examinations were carried out routinely on the first visit. The proteins were estimated quantitatively by immunochemical plasma-electrophoresis using the 'rocket method' (Laurell, 1966).

The principle of the method is that the antigen (for example, IgM) is subjected to electrophoresis in a gel containing the specific antibody concerned. The distance from application hole to peak of the rocket is measured and compared with the peak height of a corresponding antigen standard.

Neither age nor sex variations were shown for any of the three immunoglobulin categories in 99 normal subjects (Weeke, 1968).

The following normal values were employed in the present report:

Albumin: 36–51 g/l, IgG: 5·8–14·3 g/l, IgA: 0·6–3·4 g/l, IgM: 0·3–1·5 g/l.

These figures represent a 95 per cent range using our own method developed on blood donors.

Result

Abnormal immunoglobulin levels were found in some patients with endogenous uveitis. Levels of IgM were raised in 10 per cent, IgA in 17 per cent,

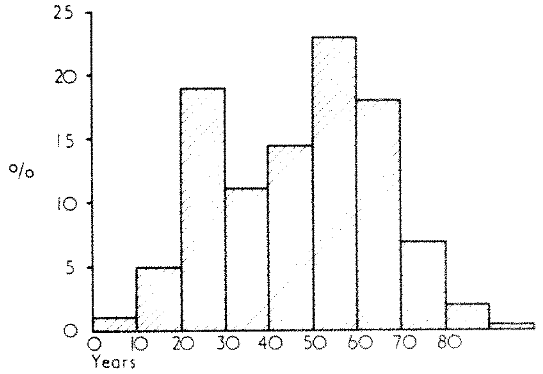

FIGURE *Age incidence in 300 patients with endogenous uveitis*

Address for reprints: M. S. Norn, MD, Eye Department, Kommunehospitalet, DK-1399, Copenhagen, Denmark

and IgG in 24 per cent. In 39 per cent of patients one or more of these immunoglobulins showed pathologically raised levels.

The uveitis series under review did not therefore confirm Aronson's observation of a particularly high incidence of raised IgM. In this series levels of IgA, and especially IgG, were more often raised than levels of IgM.

Lowered levels were found for IgM in 7 per cent, IgA in 1 per cent, and IgG in 0·3 per cent of the 300 patients examined.

UVEITIS TYPE

The immunoglobulin level was more often raised in relation to anterior uveitis than to the posterior form (Table I). In the group of patients with anterior uveitis 44 per cent showed an increase in one immunoglobulin or more, compared with 24 per cent of the group with posterior uveitis (Student's *t* test, P < 0·01).

The results in fibrinous iritis were the same as in the other anterior uveitis cases. This was unlike the erythrocyte sedimentation rate (ESR) which was found to be raised, particularly in cases of fibrinous iritis (70 per cent compared with 48 per cent in cases of non-granulomatous iritis, P < 0·01).

The difference between anterior and posterior uveitis was particularly marked for IgA (21 per cent raised in anterior uveitis compared with 5 per cent in posterior) and for IgG (27 compared with 14 per cent), but not for IgM (11 compared with 9 per cent), raised levels of which were evenly distributed within the individual diagnostic groups.

Elevated immunoglobulin levels were found more frequently in cases in which the uveitis was associated with a general disease than in cases in which uveitis alone was present.

Thus, raised levels were measured for one immunoglobulin or more in 60 per cent of 45 patients having general diseases (chronic rheumatoid arthritis, spondylarthritis ankylopoietica, tuberculosis, syphilis, or gonorrhoea) compared with only 35 per cent of the remaining 255 cases (P < 0·01).

Table I *Raised values for immunoglobulin A, G, or M in relation to different uveitis types (percentages)*

Uveitis	*Immuno-globulin**	*IgG*	*IgA*	*IgM*	*Patients (no.)*
Acute fibrinous iritis	40	24	18	12	68
Non-granulomatous subacute iritis	51	30	25	11	83
Granulomatous iritis	52	38	19	5	21
Glaucomatous iritis	53	37	27	11	19
Hypopyon, panophthalmia	24	15	15	12	33
Choroiditis centralis	24	13	7	7	45
Choroiditis juxtapapillaris	15	0	0	12	8
Peripheral choroiditis	30	22	4	13	23
Total	39	24	17	10	300

*One or more immunoglobulins raised

Neither dilated retinal veins nor optic disc oedema was found to be associated with raised immunoglobulin levels. As only 4 per cent of the total cases of uveitis had been treated with systemic steroids, such treatment would have had little influence on the results.

PROGNOSIS

Immunoglobulin levels were looked at in all patients of the series after they had been classified on the basis of the poorest visual acuity recorded during the course of the uveitis. Of patients with a visual acuity of 6/18 or less 43 per cent had raised levels of one or more immunoglobulins, compared with 35 per cent of patients who had better vision. The difference was not significant.

No correlation was noticed between number of attacks of uveitis and immunoglobulin levels.

Bilateral attacks were more often associated with elevation of one or more immunoglobulins (bilateral in 47 per cent, unilateral in 35 per cent, P < 0·05). The correlation with bilateral attacks seemed to involve IgM and IgG, but not IgA.

AGE INCIDENCE

The series was classified in 10-year age groups (Table II). All the immunoglobulins and the ESR showed a tendency to rise with increasing age. The difference was significant for IgA (20 per cent of those aged under 40 years had raised levels compared with 28 per cent aged over 40 years, P < 0·05), for one or more immunoglobulins and for ESR (31 compared with 46 per cent).

This correlation seemed to be independent of observation period, number of uveitis attacks, and type of uveitis.

Table II *Dependence of immunoglobulins on age at first uveitis attack. Figures indicate percentage of patients with raised Ig in 300 patients*

Age (years)	*Immuno-globulin**	*IgG*	*IgA*	*IgM*	*ESR*	*Patients (no.)*
< 20	31	17	7	7	33	29
20	30	19	16	6	23	67
30	33	23	6	10	54	48
40	40	24	14	14	50	42
50	44	20	28	16	42	50
60	44	35	14	7	56	43
≥70	67	38	43	14	86	21

*One or more immunoglobulins raised

OTHER FINDINGS

Table III shows the other findings in the proteinogram. No relationship was demonstrable between lowered immunoglobulin or altered albumin, alpha or beta globulin, and type of uveitis or prognosis.

The relationship of ESR with immunoglobulins is shown in Table IV. There was a positive correlation between raised ESR and raised levels of IgG ($P < 0·01$), IgA ($P < 0·01$), and an increase in one or more immunoglobulins ($P < 0·001$), whereas no significant correlation was seen with IgM.

Discussion

The present study of unselected cases of endogenous uveitis material did not confirm the hypothesis of Aronson (1968) that IgM played a central role in uveitis. The examinations showed that all immunoglobulins might show raised levels, although IgM did so more rarely than IgG and IgA.

Table III *Proteinogram in endogenous uveitis (percentage of* 300 *patients)*

Levels	*Total protein*	*Albumin*	α_1	α_2	β_1	β_2	*IgG*	*IgA*	*IgM*
Raised	20	3	6	8	3	13	24	17	10
Lowered	0	8	1	1	0	0	0·3	1	7

Table IV *Relationship between raised ESR (female* > 15, *male* > 10 *mm/h) and raised immunoglobulin (percentage of patients)*

ESR	*IgG*	*IgA*	*IgM*	*Immunoglobulin**	*Patients (no.)*
Raised	35	27	13	53	135
Normal	15	9	8	28	165

*One or more immunoglobulins raised

The investigation showed a certain relationship between raised immunoglobulin and type of uveitis (more often raised in anterior uveitis). However, any prognostic conclusions from the proteinogram would be unjustified, except that there was a greater risk of bilaterality.

The simple ESR is, perhaps, more reliably correlated with uveitis type (especially fibrinous iritis) and uveitis prognosis than immunoglobulins (Norn, 1969). A positive correlation was detected between raised ESR and immunoglobulins. Changes in immunoglobulins did not seem to be a factor related to uveitis type and prognosis.

The simple, cheap laboratory ESR test is possibly of greater practical importance in endogenous uveitis than electrophoresis as performed in the present study. On the other hand, it is worth pointing out that in some cases a raised fraction might suggest a general disease underlying the diagnosed uveitis attack.

Summary

Examination of 300 patients suffering from endogenous uveitis revealed raised levels of IgG in 24 per cent, IgA in 17 per cent, and IgM in 10 per cent.

A raised level of one or more immunoglobulins was found more frequently in anterior uveitis than in the posterior form (44 compared with 24 per cent), in bilateral cases (47 compared with 35 per cent), and in relation to certain general diseases.

No differences were demonstrated within the individual types of uveitis (fibrinous, nodular, etc.), nor was there any difference in prognosis (recurrence rate, visual impairment). Immunoglobulin levels were raised most often in elderly patients.

I wish to thank Miss Elly Norup Sørensen for practical aid.

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Immunoglobulins in tears of normal Indian people

D. K. SEN, G. S. SARIN, K. MANI, AND KUNAL SAHA*
From the Departments of Ophthalmology and Bacteriology, Maulana Azad Medical College and Associated Irwin and G.B. Pant Hospitals, New Delhi, India*

The presence of immunoglobulin-containing plasma cells in the various epithelial tissues of the body suggests a distinct secretory immunological system (Tomasi and Bienenstock, 1968). Immunoglobulins are found in body secretions. They may be important local agents of the host defence mechanism in initial or recurrent bacterial, viral, or other infectious processes (Little, Centifanto, and Kaufman, 1969). IgA is the dominant immunoglobulin among external secretions but smaller amounts of IgG and IgM may be present (Chodirker and Tomasi, 1963; Little and others, 1969; Kühl and Albrecht v. Graefes, 1971; Brauninger and Centifanto, 1971; McClellan, Whitney, Newman, and Allansmith, 1973).

Tears continuously bathe the cornea and conjunctiva. A change in their composition may be associated with local pathological changes (Josephson and Weiner, 1968). The conjunctiva and associated lacrimal glands, like all other mucosal tissues which are exposed to the environment, have substantial collections of lymphoid elements (Knoph, Blaklow, Glassman, Cline, and Wong, 1971). These synthesize immunoglobulins which are secreted into the tears. However, the immunoglobulin levels in tears have not been so extensively studied as certain other external secretions. The few reports available are conflicting. The present study was undertaken primarily to determine the immunoglobulin levels in the tears of normal Indian people and to compare them with those reported in Western people.

Subjects and methods

Tears were collected from 50 persons without any ocular or systemic disease. The eyes and ocular adnexa were carefully examined under magnification with a slit lamp and the fundus was examined by one of us (DKS) with both direct and indirect ophthalmoscopy after full dilatation of the pupil. The systemic examinations were carried out by a senior resident (KM). Only people who were normal in all respects were included in the study. They were mostly adults although the age range was 14 to 50 years (mean 30·1 years). There were 37 males and 13 females.

The subjects were asked to stare at a strong light from a slit lamp for some time. When tears had collected in the lower cul-de-sac they were drawn into a micropipette by capillary action. Care was taken not to damage the conjunctiva. The tears were expressed from the pipette into small screw-capped vials. The samples in each case were collected from both eyes and pooled; the volume ranged from 100 to 200 µl. The pooled samples were stored at -4°C until needed.

The IgA, IgD, IgG, and IgM in the samples were measured by a single radial immunodiffusion method (Mancini, Carbonera, and Heremans, 1965) using monospecific goat antisera against heavy-chain human IgA, IgD, IgG, and IgM, and the reference standards of IgD, IgG, and IgM were obtained from Meloy Laboratories, Virginia, USA. The reference standard of secretory IgA, prepared from human colostrum, was kindly donated by Dr R. Thompson, Birmingham, England.

Results

IgA was invariably found in all the samples. The mean level was 24·6±14·8 mg/100 ml. There was no significant difference statistically ($P < 0{\cdot}6$) between tear IgA level in males (23·6±15·9 mg/100 ml) and that in females (26·4±14·3 mg/100 ml), although the levels in females tended to be higher (Fig. 1). The distribution of IgA level in different age groups is shown in Fig. 2. IgA levels in the age groups were: 10 to 20 years, 28·6±9·8 mg/100 ml; 21 to 30 years, 28·0±27·2 mg/100 ml; 31 to 40 years, 19·5±10·4 mg/100 ml; and 41 to 50 years, 20·7±7·1 mg/100 ml. The difference between the tear IgA levels in the various age groups was not significant.

IgD was not found in any of the samples. IgG was very low in most, being less than 1 mg/100 ml in 42 and absent in the remaining 8. IgM was absent except in one sample, in which it was less than 1 mg/100 ml.

Discussion

IgA was the predominant immunoglobulin in the normal human tears we studied. Most other authors

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Address for reprints: Dr D. K. Sen, Department of Ophthalmology, Maulana Azad Medical College and Associated Irwin and G.B. Pant Hospitals, New Delhi-110002, India

have found the same (Table) except Bazzi, Cattaneo, Migone, and Farina (1970), who found IgG to be predominant, and McClellan and others (1973), who found the levels of IgA and IgG to be almost equal.

The IgA level in our study is comparable to the findings of other authors except Chodirker and Tomasi (1963). Statistical analysis of IgA levels in different age groups shows that the IgA level tends to be higher in younger than in older people, whereas in serum it is significantly higher in older people (Schwick and Becker, 1969). The level of IgA in tears in our study is also comparable with that reported in other body secretions. In jejunal juice it is 21·2 mg/100 ml (Douglas, Crabbe, and Hobbs, 1970); in saliva 19·4 mg/100 ml (Brandtzaeg, 1971); and in bronchial secretion 23·6 mg/100 ml (Deuschl and Johansson, 1974).

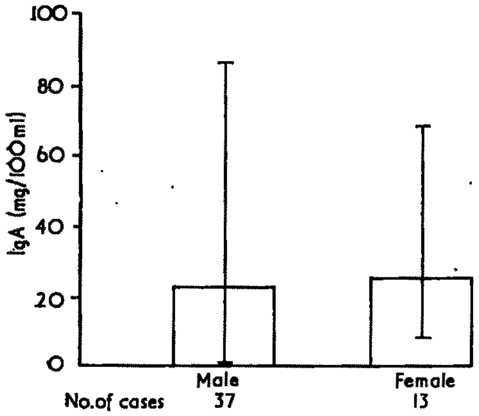

FIG. 1 *Sex distribution of IgA in tears (mean and range)*

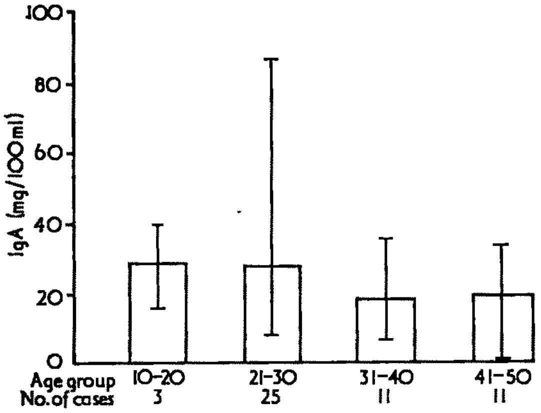

FIG. 2 *IgA in tears in different age groups (mean and range)*

Table *Reported levels (mg/100 ml) of immunoglobulin in tears of normal subjects*

Author	*Year*	*No. of subjects*	*IgA*	*IgD*	*IgG*	*IgM*
Chodirker and Tomasi	1963	7	7	NS	—	NS
Bracciolini (after onion vapour stimulation)	1968	40	24	NS	Tr	—
Barnett	1968	6	31	NS	3	1
Little, Centifanto, and Kaufman	1969	10	21	NS	Tr	NS
Bazzi, Cattaneo, Migone, and Farina	1970	9	23	NS	79	—
Brauninger and Centifanto	1971	24	9–50	NS	NS	NS
McClellan, Whitney, Newman, and Allansmith	1973	74	17	—	14	—
Present study	1975	50	24·6	—	Tr*	—†

NS = not studied. Tr = trace

* < 1 mg/100 ml in 42 samples studied

† < 1 mg/100 ml present in one subject

The only other report on IgD levels available to us is that of McClellan and others (1973), and they also noted it to be absent. IgG was present in very low concentrations in our series, which is in agreement with Chodirker and Tomasi (1963), Bracciolini (1968), and Little and others (1969). However, McClellan and others (1973) found it to be 14 mg/100 ml, and Bazzi and others (1970) found it to be as high as 79 mg/100 ml. We also failed to detect IgM in our samples. This agrees with Bracciolini (1968), Bazzi and others (1970), and McClellan and others (1973). Barnett (1968), however, reported an IgM level of 1 mg/100 ml in normal tears.

Summary

Immunoglobulin concentrations in tears from 50 healthy Indians aged from 14 to 50 years were measured by a standard immunodiffusion method. The levels of IgA were substantial; those of IgG were very low; and IgD and IgM were not present. The mean IgA level was 24·6 mg/100 ml.

We thank Dr K. B. Puri, junior resident in ophthalmology, for his help in collecting the tears.

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Book reviews

Aids to the Practice of Refraction. By ROBERT W. STEPHENSON. 1975. Pp. 24. Thornhill Press, Gloucester (65p)

The author intends this book for ophthalmologists. It is possibly best described as a booklet, and does not pretend to be a text on the subject. The trainee ophthalmologist inevitably finds he is required at an early stage in his career to do many quick refractions. These are often done without a background of proper theoretical or practical instruction. Later he is often forced by circumstances to do long stints of refraction, again in a hurried manner.

Thus the basis of refraction practice as an accurate diagnostic tool or its exact and correct relationship to an optical appliance is lost to the ophthalmologist. In these circumstances, the procedure becomes a bore and unrelated to the patient. This booklet raises pertinent aspects in an orderly fashion, essentially on the clinical management of patients seeking an eye examination. Since the 24 pages can be read almost at one sitting, it is sound advice that all those about to study refraction in greater depth should start with this simple outline.

MONTAGUE RUBEN

Colour Vision Test. By ROBERT J. FLETCHER. Keeler Instruments, London

The City University colour vision test has been produced by Professor Robert J. Fletcher from the Department of Ophthalmic Optics and Visual Sciences. It uses a series of selected paper colour samples, each page providing the opportunity for a normal response. The patient is asked to identify the normal 'spot' as resembling the centre spot more closely than other alternatives. The patient's choice is recorded for each page and this enables the examiner to quantify the depth of an inherited defect depending upon the number of mistakes made by the examinee. The book is smaller than the normal Ishihara chart and enclosed is a form for recording results. The test is simplicity itself if a few guide lines are followed and these are carefully explained in the introductory notes.

S. J. H. MILLER

Conference for the Prevention of Impaired Vision and Blindness, Paris 1974. (Documenta Ophthalmologica Proceedings Series, vol. 5). Edited by W. J. Holmes. 1975. Pp. 204, 158 figs, 52 tables. Junk, The Hague (DG65)

As blindness becomes increasingly a world problem it is essential that more efforts should be directed towards its prevention in the developing world. The scope of the problem is immense—20 million affected by onchocerciasis, 500 million affected by trachoma. The World Health Organization has now included the prevention of blindness in its activities and an International Association for the Prevention of Blindness has been formed. Its first meeting was at the International Congress of Ophthalmology (Paris 1974) where public health ophthalmology was accepted as being a new dimension.

The contributors are principally ophthalmologists who include in their papers work from allied specialties like genetics. There are contributors from India, Pakistan, and south east Asia where blindness is rampant. There is an excellent article on homocystinuria by François, and two important articles, one from USA and one from Israel, on the prevention and treatment of hereditary eye disease. These growing points of our knowledge include prenatal diagnosis by amniocentesis and possible lines of treatment of certain metabolic diseases like Wilson's disease and homocystinuria. The book is worth obtaining for these articles alone. It concludes with several articles on the pathogenesis of retinal vein occlusion, although no one can suggest much in the way of prevention.

C. A. BROWN

Functional Examinations in Ophthalmology, Parts I and II (Fourth Congress of the European Society of Ophthalmology, Budapest, 1972). Edited by J. FRANÇOIS. 1974. Pp. 692, 343 figs, 47 tables, refs. Karger, Basel (£30–60)

In Part I virtually all methods, both objective and subjective, now available for the investigation of ocular function are dealt with. Emphasis is laid on the importance and use of such methods in research, and also in clinical diagnosis where, for example, it is often only possible to understand and classify the multitude of choroido-retinal infections after duly considering the combined results of such tests as visual acuity, static and dynamic perimetry, disturbances of colour vision, dark adaptation, and electrodiagnostic investigations.

Part II comprises free papers which in one way or another relate to the methods now available for the investigation of ocular function.

D. GREAVES

The History and Traditions of the Moorfields Eye Hospital, vol. II. By F. W. LAW. 1975. Pp. 299, 70 illustrations. Lewis, London (£4)

Moorfields is a unique hospital; the oldest and still probably one of the largest eye hospitals in the world, it has had a major influence on ophthalmology ever since it was founded in order to cope with the trachomatous soldiers returning from the Napoleonic wars. The history of Moorfields thus reflects the whole evolution of scientific ophthalmology from the simple empirical nostra of 1805 to its present complexity, against a colourful background of medical politics and personalities. The travails and triumphs of Moorfields up to the first world war had already been recorded by Treacher Collins in 1929, but only three copies of this admirable book have evidently survived. So, by a happy arrangement, facsimiles of this earlier book have now been published with Frank Law's second volume, bringing the story up to date—or rather up to 'yesterday', since it went to press just before our last Minister of

Health took office, with the sorry happenings that have followed in her wake.

Frank Law, who has been part of Moorfields ever since the first war (when he overlapped with Treacher Collins), helping, and still continuing to help, in so many capacities, was the obvious choice of author; and the book is clear, comprehensive, and indeed a model for the future historians of our great medical institutions.

It must have been a problem to furnish a record of so much change, to catalogue the evolution of all the new departments that have emerged, to give life to all those shadowy personalities that crowded on to the stage, particularly when in 1948 the Central London Ophthalmic Hospital was engulfed, the Institute started, and the 'Royal Westminster' at High Holborn united. Thereafter the changes and emergent departments in the last are decently appended (a résumé of the history of the Royal Westminster from 1816 to 1948 would have been a welcome addition to the record). And, above all, how difficult it must have been to condense that endless stream of minutes which formed the body of the record, with their depressing official jargon, their impersonal tones and passive tenses, their prolixity and stuffiness. One is grateful for the occasional anecdote and fleeting aside. Without them (and one longs for more) it would be rather like reading Bradshaw—an important record, but undeniably heavy going. Even so the biographical sketches of the main characters tend to read like the pious obituary notices from which many of his accounts were doubtless drawn. For they all emerge as virtuous, dedicated, and orthodox; even the unlikeliest of them seems to have started with athletic prowess in some sport, and they all progressed serenely through a succession of standard achievements to an honoured retirement. It is a credit to Law's artistry that in these he manages never to repeat himself.

Every now and then one regrets that the author, who is capable of writing with such spirit and satire, such whimsy and wit, has so muted the sound of artillery over those near-forgotten battles around the Royal College chair, the amalgamation, the birth of the Faculty and so on. He might just have hinted at the foibles and shortcomings of some of the staff now long dead. But he is grave and benevolent throughout—perhaps just as well—one must not look for fun in Leviticus.

P. D. TREVOR-ROPER

International Glaucoma Symposium, Albi 1974.

Edited by R. ETIENNE and G. PATERSON. 1975. Pp. 501, fig, tables, refs. Diffusion Générale de Librarie, Marseille (£40)

This book represents the published proceedings of the International Glaucoma Symposium held in Albi in May 1974. In addition there are two extra chapters on the use of ultrasonography in glaucoma and pneumotonography. It includes contributions from experts in this field and brings the reader up to date on glaucoma. The book is particularly interesting because the discussions are published in full. It is well produced with high quality illustrations including a set of stereophotographs of the optic disc and should prove a useful addition to all ophthalmic libraries.

S. J. H. MILLER

Modern Approaches to the Diagnosis and Instruction of Multihandicapped Children, vol. 13. Eye Movements, Surprise Reactions, and Cognitive Development.

By R. M. WILTON and F. J. BOERSMA. 1974. Pp. 69, 2 figs, 6 tables, refs. University Press, Rotterdam (DG29·90)

This is not a book for the general ophthalmologist and it will be of limited interest only to those in the speciality who study the link between recorded eye movements and visual perception. Even so the objectives outlined, namely whether training can accelerate intellectual development and if retarded children differ from normal children in this respect, have little ophthalmological content.

The acceptance by the authors that corneally reflected eye movements in children can be used experimentally as an index of 'perceptual activity' might surprise those of us who deal with children. Educationalists are in a better position than ophthalmologists to judge the value of the main conclusions. These are that the development of intelligence can be accelerated in normal children by training and that visual searching of pictorial material increases with age and/or mental development. These conclusions are supported by no fewer than 11 pages of statistics.

P. A. GARDINER

Modern Problems in Ophthalmology: New Research on the Aetiology and Surgery of Retinal Detachment.

By L. GUILLAUMAUT, M. MASSIN, and L. FISONS. 1975. Pp. 138, 150 figs, 55 tables. Karger, Basel (DM145)

This book reports the ninth meeting of the proceedings of the Club Jules Gonin which was held in La Baule, France, in 1974. The book is mainly in English but contains some contributions in French and German. The many subjects dealt with included genetics in retinal detachment, the terminology and nature of peripheral retinal degeneration, the non-drainage of subretinal fluid in retinal detachment surgery, and recent advances in vitreous surgery. There were also contributions on photocoagulation. Of particular interest was the work performed by the Miami group on the pathogenesis of intraocular fibrous tissue.

The book is beautifully produced and the illustrations are of high quality. It gives a thoroughly up-to-date account of progress in the management of diseases of the retina and is recommended to ophthalmologists with a special interest in this subject, although all ophthalmologists will find it of value as a source of reference.

A. H. CHIGNELL

Modern Problems in Ophthalmology, vol. 12. Limitations and Prospects for Retinal Surgery.

Edited by E. NORTON, R. DUFOUR, C. GAILLOUD, R. KLOTI, and L. FISON. 1974. Pp. 598, 192 figs, 143 tables. Karger, Basel (£25·40)

This volume is a report of the eighth meeting of the Club Jules Gonin held in Miami in 1972.

The main subject was the cause of failure in dealing with detachments of the retina. Several papers dealt with aspects of basic research and experimental work in macular disease; others reported the clinical use of the xenon arc and argon laser in macular disorders and in diabetic retinopathy. Other papers were given on vitrectomy and the use of vitreous substitutes. A final section of the book is devoted to the diagnosis and natural course of malignant melanoma, treatment by photocoagulation and excision, and on the long term follow-up of retinoblastoma.

The extensive and interesting discussions which went on throughout the meeting are fully reported. D. GREAVES

Ocular Differential Diagnosis, 2nd ed. By F. H. ROY. 1974. Pp. 612, refs. Lea & Febiger, Philadelphia; Kimpton, London (£8·30)

This is a reference book written to help the ophthalmologist to make a quick diagnosis and to prevent his overlooking a possible disease. The book contains comprehensive lists of possible conditions described under the different parts of the eye. For example, there are 39 syndromes associated with nystagmus and 48 with congenital cataract.

The second edition has been enlarged by 144 pages, several sections have been added, including those on granulomatous and non-granulomatous uveitis, and on ultrasonography of the orbit; there are also tables of comparison. The index would be easier to use if the main reference to a disease could be italicized. Actinomyces (p. 250) is still wrongly listed under bacteria, and prematurity associated with anoxia or hypoglycaemia is not mentioned as a cause of congenital lamellar cataract.

This book is a real mine of information and should be of value to the established ophthalmologist and to juniors preparing for examinations. C. A. BROWN

The Ocular Fundus; Methods of Examination and Typical Findings, 3rd ed. By A. NOVER. 1974. Pp. 169, 150 figs. Lea & Febiger, Philadelphia; Kimpton, London (£9·25)

This third edition of a small textbook on the fundus has been translated from the German by Frederick Blodi. A chapter on diseases of the vitreous has been added for this edition.

The first part is mainly concerned with methods of examination. However, it is difficult to decide for whom the book is intended, as the descriptions are too brief for the ophthalmologist and yet not sufficiently practical for the non-ophthalmologist.

The second part is essentially a colour atlas of the fundus with a text describing the conditions, their ophthalmoscopic findings, and differential diagnosis. Colour prints of the fundus are difficult to reproduce but these are excellent and the book is recommended as an atlas to students, physicians, and junior ophthalmologists. MARTIN CRICK

Ocular Motility and Strabismus. By M. M. PARKS. 1975. Pp. 195, 150 figs, refs. Harper & Row, Hagerstown, Maryland ($25)

In the description of the contents of this book, emphasis is made on the fact that strabismus is primarily a disorder which occurs in the paediatric age group. It is scarcely surprising, therefore, that this new contribution to the subject of the disorders of ocular motility is made by such a person as Dr Marshall Parks, who has achieved world-wide recognition as a paediatric ophthalmologist with a rare ability to combine academic excellence with a great degree of practical skill.

An appraisal of the structure and function of the normal extrinsic ocular muscles is given in a clear and yet detailed way in the early chapters. This is followed by an essay on the meaning of the complex phenomenon of binocular single vision, and this leads naturally to a discussion on the different forms of squint and on the methods which are adopted in their detection. The important role of the mechanism of accommodation in the production of squint is discussed in a chapter dealing with the vergence movements of the eyes, and this includes a straightforward description of the AC/A ratio.

The sensorial adaptations in squint—suppression, amblyopia, eccentric fixation, and anomalous retinal correspondence—are dealt with in an up-to-date manner with a detailed discussion on the methods of examination which are concerned in their detection and with a realistic appraisal of their importance, particularly in regard to their prevention and treatment. This is followed by excellent chapters on the management of esodeviation, exodeviation, and vertical squint, with a separate chapter devoted to the A and V phenomena which are features of many basically horizontal squints. There are also descriptions of the squints which follow cranial nerve palsies, congenital anomalies, and various forms of trauma.

The book is of a remarkably non-controversial nature. Certain parts, particularly the discussions on the monofixation syndrome and intermittent exotropia, reveal the personal views of the author, but these have been acquired as the result of prolonged experience and the contrasting opinions are included in the discussion. Indeed, the text as a whole provides 'a breath of fresh air' in a field of ophthalmic practice which tends to be obscured sometimes by an unnecessary obsession over tedious detail so that the main aim in the treatment of squint in the young child—the achievement of a satisfactory form of binocular association—tends to be overlooked in the frequently fruitless task of trying to achieve a state of perfection. KENNETH WYBAR

Ocular Pathology: A Text and Atlas. By M. YANOFF and B. S. FINE. 1975. Pp. 762, figs (25 in colour), refs. Harper & Row, Hagerstown, Maryland ($60·00)

Having previously provided a superb account of the normal structure of the eye, Dr Yanoff and Dr Fine have now produced an equally masterly survey of ocular histopathology. The coverage is comprehensive with virtually no ocular disorder escaping mention, and the authors are to be envied in their ability to depict so many of the conditions they describe. By dint of careful montage and judicious pruning of all but the immediately relevant areas, an incredibly lavish array of photographs has been included and, on the basis that one good illustration conveys more than a barrage of words, the book provides considerably more information than its size would suggest. Unfortunately, however, the reduction in size of some photographs, which the inclusion of such a large number has necessitated, has in some instances also reduced their value.

The text is essentially descriptive and is presented in notation form—which makes for ready reference if not for easy reading—so that for a discussion on the aetiology and pathogenesis of most conditions recourse to the original papers and reviews listed at the end of each chapter is imperative. Coming from the pens of practising ophthalmologists there is a welcome emphasis on clinicopathological correlation, a quality which should extend its appeal.

Although there are a few statements with which one might take issue, factual errors are few. There is no good evidence that T-lymphocytes produce antibody and that the ciliary body cysts in multiple myeloma contain gamma rather than alpha globulin.

For a straightforward account of ocular pathology, detailing both light and electron microscopical appearances, this text and atlas is the obvious choice, other books on the same subject being either outdated or less comprehensive, and it can enthusiastically be recommended. Its only drawback for the individual buyer is its price.

A. GARNER

Practical Cryosurgery. Edited by H. B. HOLDEN. 1975. Pp. 168, figs, tables, refs. Pitman, London (£5)

Harold Holden, the editor of this volume, has collected authors whose experience of cryotherapy is pre-eminent in each of the fields of treatment discussed. Reference to his own work is made in the chapters on the nose and throat and on the head and neck.

The history and development of cryosurgery and cryosurgical engineering are considered with sufficient detail to interest the reader, although he will be concerned chiefly with the chapters dealing with his own field.

Cryosurgery is described in relation to the majority of its potential uses, and each chapter has an up-to-date and adequate list of references for further reading.

Schoeller introduced cryotherapy experimentally in the treatment of retinal lesions as long ago as 1918, and Bietti described its clinical use in 1934. Cryotherapy is now firmly established as an important technique in ophthalmic surgery. Its wide application in the treatment of conditions affecting most of the ocular tissues is adequately considered. The ophthalmologist will find, either in the text or in the references, all the information he requires to pursue this branch of treatment.

J. R. HUDSON

Selected Topics on the Eye in Systemic Disease. Edited by S. J. RYAN and R. E. SMITH. 1974. Pp. 392, figs, tables, refs. Grune & Stratton, New York (£11·75)

This is an excellent book, and one to be read at length as well as being a useful work of reference. It is not a collection of original work, but a selection from a course of lectures given at the Wilmer Institute. It is divided into three sections: Retinal vascular disease, Ocular inflammatory disease, and Rheumatic disease in which are included connective-tissue disorders and arthritis.

Although written by a large number of contributors the style is uniformly good. The English is clear and careful and the presentation suitably brief but comprehensive. A chapter on the systemic manifestations of the condition under discussion is followed by one on the ocular manifestation of the same pathological process. It may be invidious to select specific chapters for special praise but I particularly enjoyed the discussion on diabetic retinopathy, sarcoidosis, and histoplasmosis. The uniformly high standard of the contributions is a tribute to the skill and persuasiveness of the editors. The volume is well produced and the illustrations are clear.

C. J. EARL

Studies on Excitation and Inhibition in the Retina (a collection of papers from the laboratories of H. Keffer Hartline). Edited by F. RATCLIFF. 1974. Pp. 668, figs, tables, refs. Chapman & Hall, London (£10·50)

The idea of reprinting a series of previously published articles is not new and the soundness of such a course is often doubtful. No such doubt can befall this most excellent book. All ophthalmologists will have heard of Professor Hartline although many may be less familiar with his work. The foreword to this collection of papers is written by Professor Hartline who modestly implies that his choice of *Limulus polyphemus* as an experimental animal was a lucky chance. More than 40 years ago he started his experimental work which has given us so much information about the peripheral visual system.

There are five sections in this collection, each covering a particular aspect of visual physiology and comprising reprints of papers by Hartline or his co-workers in mainly chronological order showing how the line of research has been developed. Each section is preceded by a review excellently written by the editor. The book ends with Hartline's own review of his work given as his Nobel Prize speech in 1967.

This is not a book the clinician will buy but he will surely be impressed by seeing, in Hartline's own words, that the merit of publication 'lies in exhibiting a short segment of a thread of work that is now woven almost unrecognizably into the fabric of visual science'. It is a fitting tribute to one of the leaders of visual physiology and not marred by a printing slip from pages 410–411. The clarity of these papers will serve as a model to present-day authors.

J. H. KELSEY

Brit. J. Ophthal. (1976) **60**, 309

Obituary

William John Brownlow Riddell, FRS, MD, ChB, FRFPS, DOMS

W. J. B. Riddell, Emeritus Tennent Professor of Ophthalmology at the University of Glasgow, died suddenly on 18 February 1976 while on holiday in Austria. He was in his 78th year.

Brought up in Glasgow where his father was visiting ophthalmic surgeon to the Eye Infirmary, he received his education at Glasgow Academy, and thereafter was commissioned in the Royal Naval Volunteeer Reserve, serving at sea as midshipman for the last year of the first world war. After demobilization he chose a medical career and graduated MB, ChB at Glasgow University in 1923. In the very unsettled years after the war, he held a succession of junior posts and gradually became orientated towards ophthalmology, adding the qualifications DOMS London in 1928, and FRFPS Glasgow in 1936, until finally he went to the Royal London Ophthalmic Hospital to pursue his chosen specialty. He then returned to Glasgow as surgeon to the Ophthalmic Institute of Glasgow Royal Infirmary, and in 1940 he presented a thesis based on his research in human heredity which was receiving international recognition, and was awarded MD with high commendation.

In 1941 he was appointed to the Tennent Chair of Ophthalmology at the University of Glasgow. The Tennent Institute, completed in 1936, had been designed with the dual purpose of providing university teaching and research facilities while also serving as the eye department of a large general hospital, the Western Infirmary. He had to defer his plans for research and staffing his new department owing to the exigencies of the second world war, but with characteristic foresight he began to assemble the nucleus of what proved to be an outstanding reference library. In addition to sustaining the needs of his hospital and private practices, he so organized his time as to allow regular visits to London where he served on the ophthalmic panel formed to advise the Ministry of Supply on the effects of chemical warfare agents on the eye. He also accepted the additional duty of Dean of the Faculty of Medicine for the University of Glasgow; in this capacity he visited North America in the immediate postwar period and was invited to lecture on his specialty at many university centres. The inception of the National Health Service in 1948 presented him with a role for his administrative ability which was ably demonstrated over a long period on the board of management of Glasgow Western Hospitals; he was also president for more than 20 years of the Mission to the Outdoor Blind for Glasgow and the West of Scotland. His many other offices included the presidency of the ophthalmological section of the Royal Society of Medicine, the vice-presidency of the Ophthalmological Society of the United Kingdom, and the vice-presidency of the Faculty of Ophthalmologists. He retired from the Chair after 23 years of distinguished service in 1964, relinquished his appointment as senior ophthalmic consultant to the Western Infirmary, and ceased all active practice.

Professor Riddell was scrupulous in all he undertook. A perfectionist in his own surgical technique, he set a high standard in his training of others and passed on his skills to many postgraduate students. He could express himself concisely and cogently, and was adept in selecting the most suitable form of illustration and presentation of a subject; his criticism of the work of others was always generous and helpful. An agile mind, his width of reading and ability to marshal and analyse facts rapidly, enabled him to make an incisive contribution to the discussion of many topics. He was a stimulating companion during his occasional leisure hours, whether watching cricket, strolling through a park, or browsing in a gallery or museum. Visitors were always made welcome at his home, and many in various parts of the world will carry with them the memory of the generous and warm hospitality they received on visiting Bill Riddell and his charming wife, Nan.

After retiring in 1964, he went to live in Aberdeen, where his family roots lay. This environment supplied an aura of university life which he found congenial, but was also becoming enfused with new cultural activities which served to occupy the interests of a nature always active. Survived by his wife, a son, and a daughter who is a consultant pathologist, he was an outstanding specialist of his generation.

Sir Tudor Thomas, DSC, MD, FRCS, LLD

Wales and ophthalmology have lost one of their great medical personalities in the death of Sir Tudor Thomas at the age of 82.

He was born in Breconshire but spent most of his professional life in Cardiff where he was much esteemed by his colleagues and many friends.

His academic achievements were many, for as well as winning prizes as a student at Cardiff University and at the Middlesex Hospital, he gained most of the degrees possible to a graduate. Later he had an Honorary LLD conferred on him by Glasgow University. He served in the RAMC in the first world war and in 1921 was appointed ophthalmic surgeon to the Cardiff Royal Infirmary and United Cardiff Hospitals which he served for 37 years.

He sprang to fame in 1922 by becoming the pioneer of research work in this country on corneal grafting; he demonstrated clear grafts on rabbits' corneae in 1930 at a London meeting and later that year he performed his first corneal graft on man. The Central London Ophthalmic Hospital invited him to establish a corneoplastic department at their hospital in 1935; this department continued until 1940. He had great help and encouragement from the Staff of both Moorfields and the Royal Westminster Ophthalmic Hospitals.

Many professional societies honoured him. In 1933 he delivered the Middlemore Lecture at the Birmingham Eye Hospital and in 1936 the Montgomery Lecture in Dublin. He took a keen interest in the work of the British Medical Association and was honoured by being elected President in 1953–54 and gave a masterly inaugural lecture.

In 1955 he gave the Doyne Memorial Lecture at his favourite Oxford Ophthalmological Congress on whose council he had sat for many years. From 1956–58 he presided as Master with innate charm and quiet dignity—these being three very happy years for him, his wife, and members. His contributions and chairmanship made these meetings a great success. By a fortunate coincidence he was Knighted during this term of office and at his beloved Oxford Congress Lady Bronwen organized the lady visitors' social programme.

In 1956 Tudor was elected High Sheriff of Breconshire and it gave him pleasure to entertain prominent Breconshire and Cardiff personalities to an inaugural luncheon.

The Worshipful Company of Apothecaries honoured him by presenting their Gold Medal in therapeutics to him in 1960 and he was elected an honorary member of the Royal Society of Medicine later.

At the age of 72 he was invited to be President of the Ophthalmological Society of the United Kingdom in 1967–68 and one of the meetings was held in Cardiff.

Seemingly destined to be a bachelor, in 1938 he married a young vivacious Welsh lady, Bronwen Pugh, and it is true to say she greatly enlivened his social life. They had two sons, David in law and William in general practice.

With all the brilliance of his academic and professional career, he was a gentle and kind man with great personal charm and dignity and a quiet sense of humour. The ophthalmological world has lost a great man whose memory many will treasure.

Notes

Eye-Bank Association of America, Inc

Las Vegas, 5 *October* 1976

The Eye-Bank Association of America will hold a scientific programme on 5 October 1976, from 1.00 to 5.00 pm. Papers relating to corneal transplantation and eye bank techniques are solicited.

For further information write to R. D. Richards, MD, Department of Ophthalmology, University of Maryland Hospital, Baltimore, Maryland 21201, USA.

Course in Microsurgery

Nantes, 10 *to* 11 *December* 1976

The fourth practical course in microsurgery will be directed by Professor Witmer of Zurich and will concern the surgical techniques for operations of intra- and extracapsular extraction. Applications should be made by the 30 June to the Secretary, 16 Boulevard Guist'hau, Nantes.

Scientific Meeting

Cairo, 4 *to* 8 *March* 1977

The Ophthalmological Society of Egypt will arrange a scientific meeting on the occasion of its diamond jubilee.

For further information write to the Honorary Secretary, Ophthalmological Society of Egypt, Dar El-Hekma, 42 Kasr El Aini Str., Cairo, Egypt.

Jerusalem Conference on Impaired Vision in Childhood: Causes, Prevention, Treatment

Jerusalem, 8 *to* 13 *May* 1977

For further information write to Scientific Secretariat, Professor J. Nawratzki, PO Box 16271, Tel-Aviv, Israel.

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The author should make adequate reference to previous work on his subject, and provide a full summary of his observations and conclusions.

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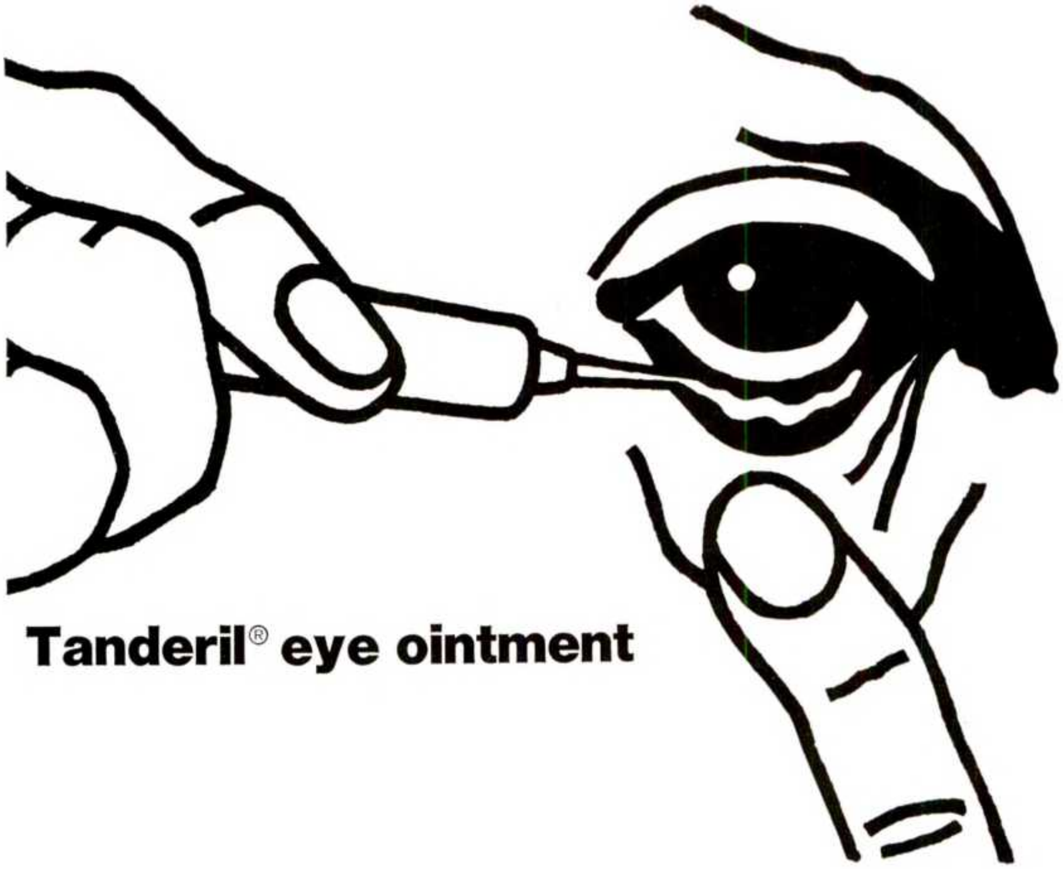

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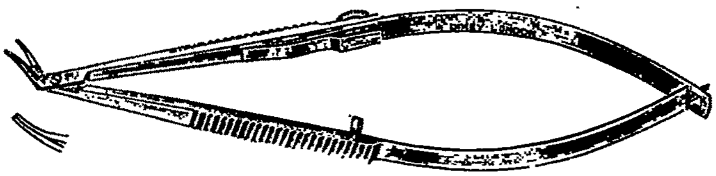

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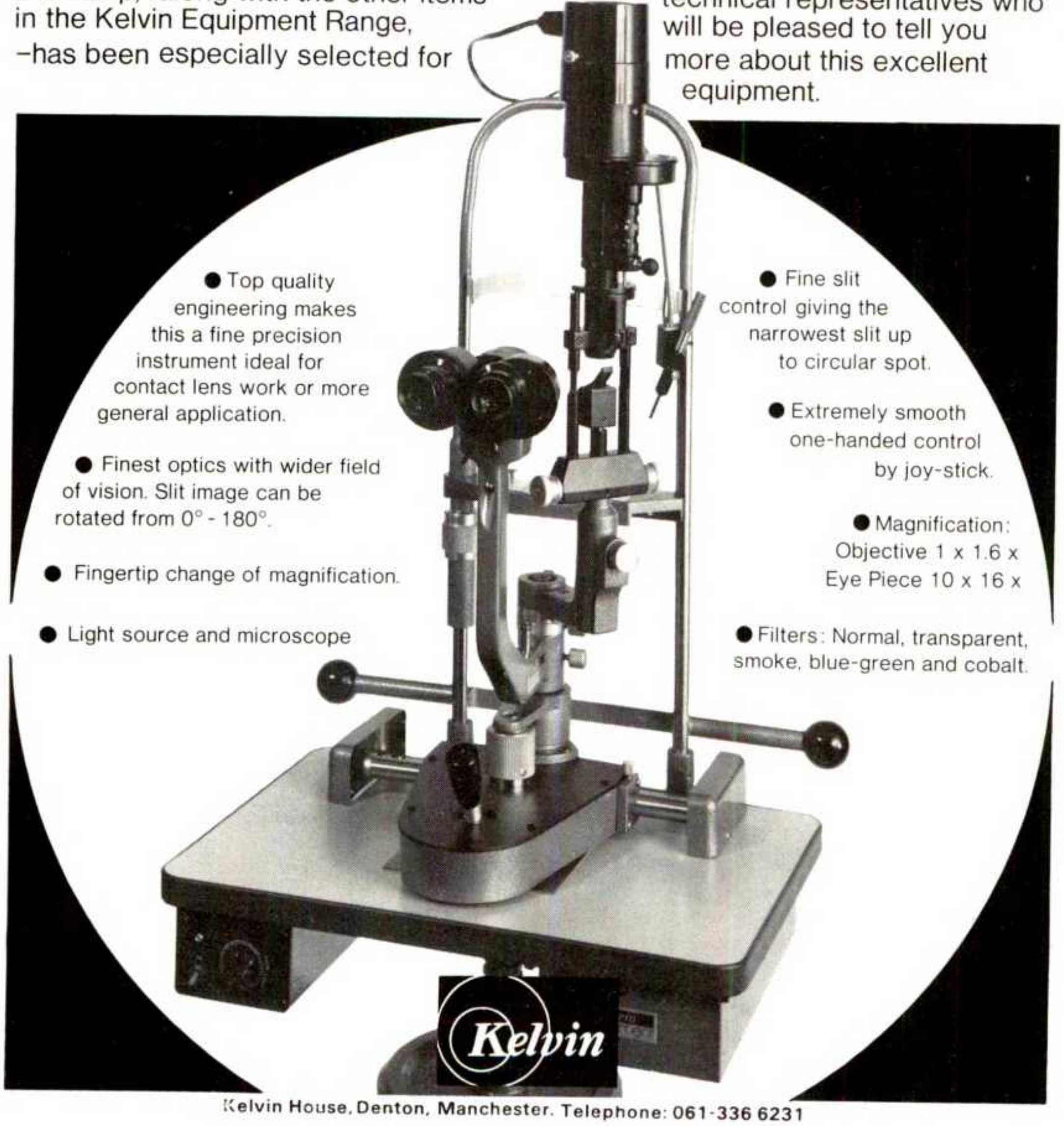

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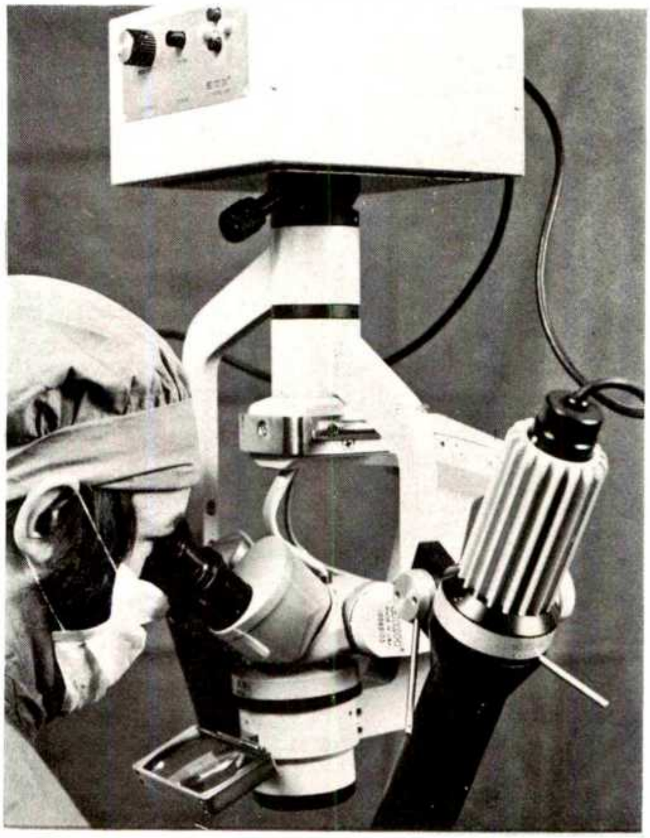

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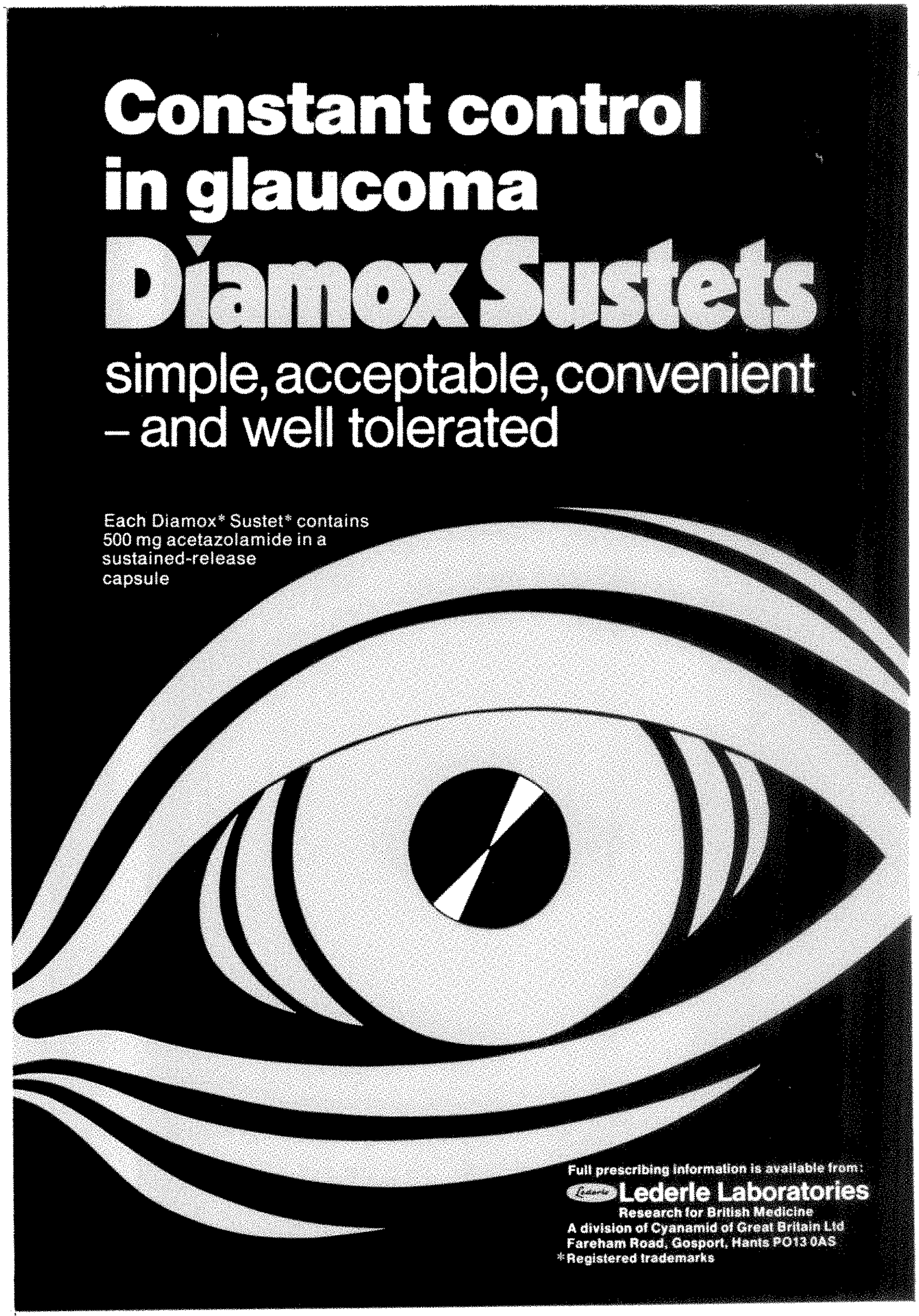

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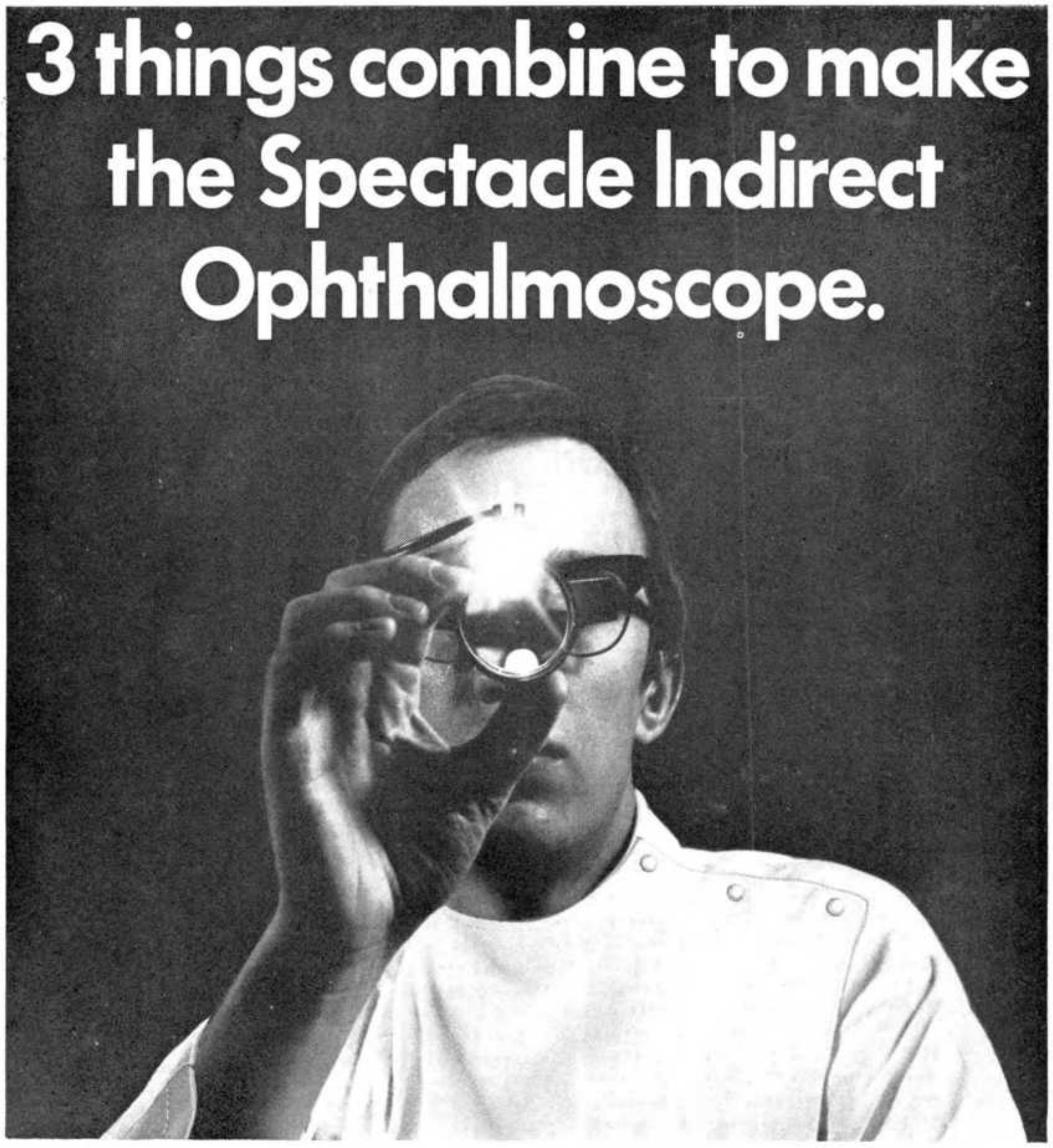
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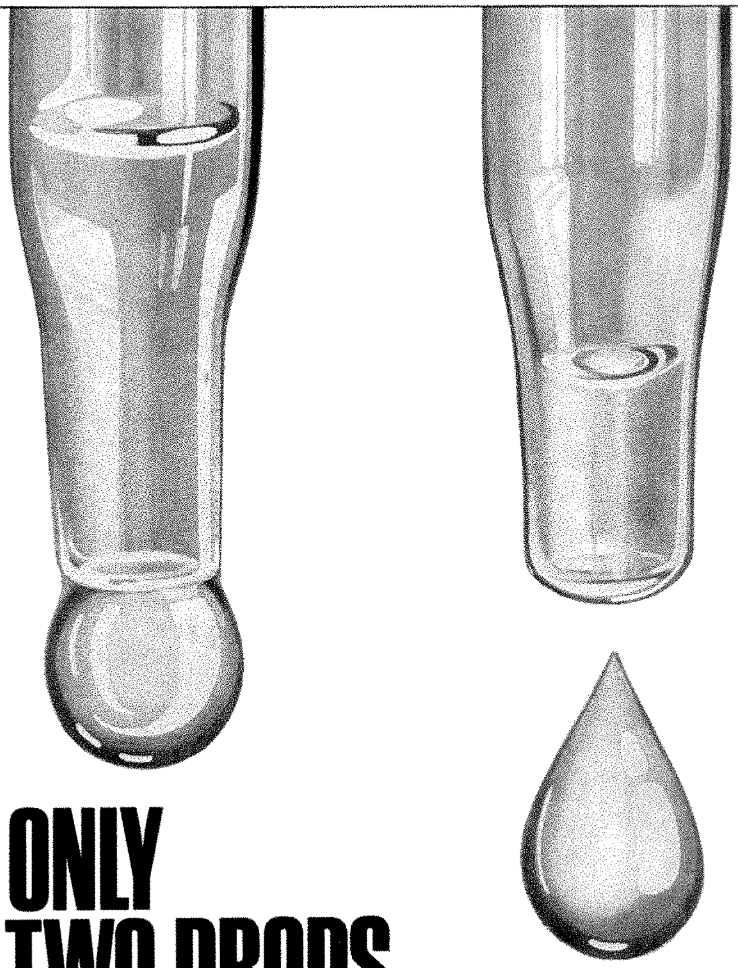

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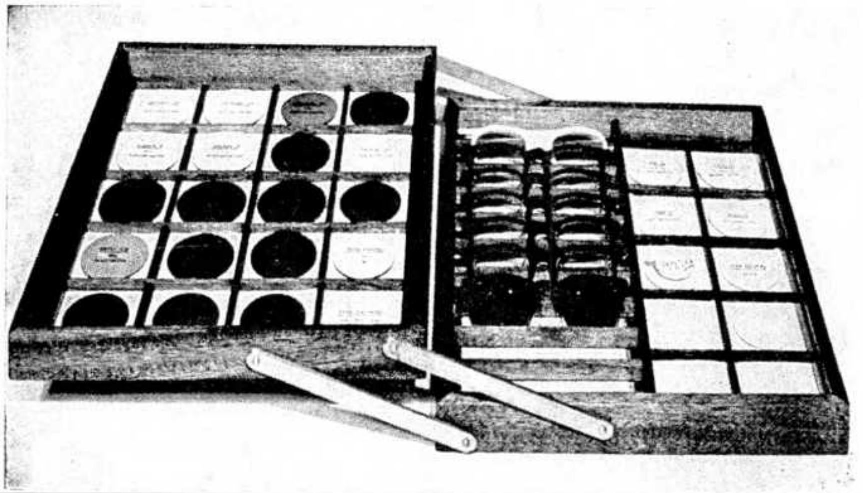

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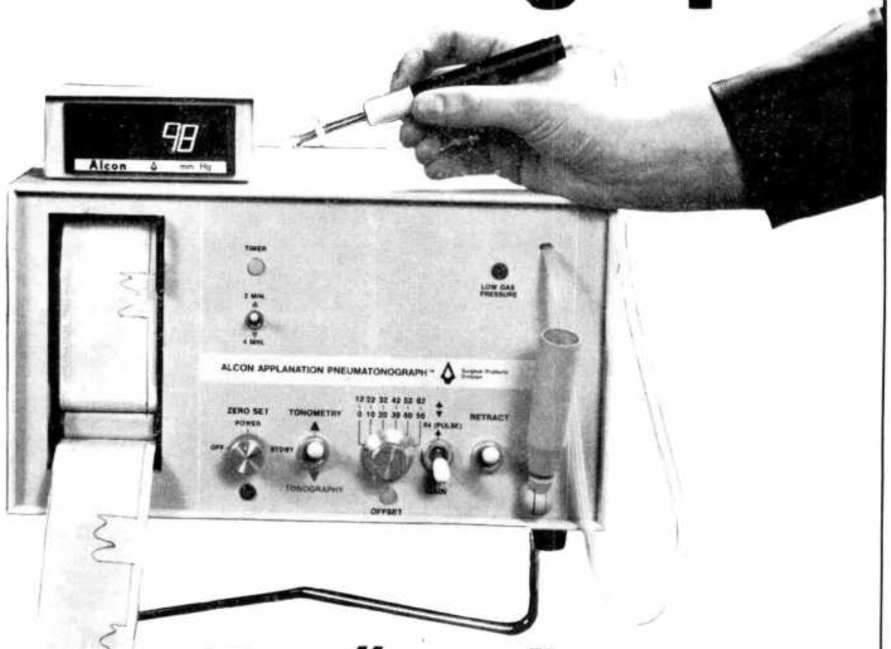

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Editorial: Beta-blockers and the eye

Beta adreno-receptor blockers have been in clinical use for more than 10 years and during this time they have proved valuable in the control of hypertension, angina, and dysrhythmias. Drugs with increasing selectivity have been introduced to allow control of cardiac receptors without producing unwanted side-effects from peripheral vascular disturbances or bronchospasm. Practolol was such a cardioselective beta-blocker which became available for general clinical use in 1970. During 1974 a unique clinical syndrome was described (Felix, Ive, and Dahl, 1974; Wright, 1974, 1975) in which a very small number of patients, less than 0·5 per cent of all treated with the drug, developed skin rashes, dry eyes with distinctive corneal and conjunctival signs, secretory otitis, and fibrous thickening of serous membranes leading to a fibrosing peritonitis and small bowel obstruction. These clinical signs were associated with the development of antinuclear antibodies and an antibody attaching to intercellular determinants (Amos, Brigden, and McKerron, 1975).

The most recent account of the histopathology confirms the distinctive features of the syndrome and clearly shows that it is not just another dry-eyed state, but that it is a fibrosing polyserositis with immunological and ocular aspects (Rahi, Chapman, Garner, and Wright, 1976).

After descriptions had been published on the adverse reaction attributed to practolol, a small number of case reports appeared suggesting that various minor ocular symptoms and signs were related to administration of beta-blockers other than practolol. In all cases the symptoms and signs were non-specific and none showed the unique features of the practolol-induced syndrome.

Patients needing this group of drugs are of an age when involution of the lacrimal gland, lid conditions–such as disorders of position of the lid edge or chronic infection–may produce minor and variable symptoms (Wright, 1976). It would seem quite impossible to link such non-specific complaints with administration of any drug and it would be unreasonable to compare them in any way with the very specific features of the practolol adverse reaction, particularly since it has been shown that patients suffering from the practolol-induced skin reaction suffer no cross-reactivity or clinical exacerbation on treatment with another beta-blocker (Felix, Ive, and Dahl, 1975).

Recent work has suggested that beta blockade may prove useful in the reduction of intraocular pressure although its exact place in the treatment of glaucoma has not yet been clearly defined.

Beta-blockers have proved a valuable group of drugs and although one has been shown to cause an adverse reaction there would seem to be no reason at present to incriminate all this group of compounds or to deny any patient treatment which promises to prolong or improve the quality of life.

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Pathology of practolol-induced ocular toxicity

A. H. S. RAHI*, C. M. CHAPMAN†, A. GARNER*, AND P. WRIGHT†
From the Institute of Ophthalmology and Moorfields Eye Hospital†, London*

Practolol is a potent beta-adrenergic receptor blocking drug widely used in the management of angina pectoris, cardiac dysrhythmias, and systemic hypertension. Its immediate side-effects are usually trivial but latterly, as a result of prolonged administration, there have been several reports of more serious complications affecting multiple systems. Skin rashes, chiefly psoriasiform and erythematous with associated hyperkeratosis of the plantar, palmar, and digital surfaces, appear to be the most common disturbance (Felix, Ive, and Dahl, 1974; Wright, 1975), but conduction deafness (Wright, 1975) and intestinal obstruction secondary to a peculiar sclerosing peritonitis (Brown, Baddeley, Read, Davies, and McGarry, 1974; Meyboom, 1975), are also well known. Dryness of the mouth and nasal passages has been described and, exceptionally, a syndrome comparable to systemic lupus erythematosus with fever, nephropathy, and joint pains has been observed (Raftery and Denman, 1973).

The incidence of ocular lesions attributable to practolol is second only to that of skin changes. After a brief preliminary report (Wright, 1974), the clinical features of the eye changes were recorded in detail (Wright, 1975), and it was noted that all patients presented with the signs and symptoms of a dry eye which later progressed to an unusual form of conjunctival fibrosis. In some patients corneal opacities and severe ulceration developed. Although the pathogenesis is far from clear, immunological mechanisms may be involved. Several workers (Amos, Brigden, and McKerron, 1975; Rahi and Garner, in press) have identified antibodies with an affinity for the intercellular component of squamous epithelium as well as antinuclear factors and autoantibodies to smooth muscle.

We report here the ocular pathology in six patients with lesions attributable to practolol toxicity together with the results of antibody-labelling studies.

Case reports

CASE 1

A 75-year-old man, with angina following myocardial infarction, was treated with practolol for two and a half years. After two years' medication he developed skin eruptions and dry eyes with subconjunctival fibrosis causing entropion and requiring surgery to the lids on the right side. Subsequently the patient died as a result of further, sudden myocardial infarction.

Histopathology

Sections of the enucleated globe showed moderately severe acanthosis of the conjunctival epithelium and complete absence of goblet cells with mild leucocytic infiltration of the underlying connective tissue (Fig. 1). On one side there was also some acanthosis of the corneal epithelium associated with destruction of Bowman's membrane and the formation of a subepithelial vascular pannus. Over much of the cornea, however, the epithelium was reduced in thickness and showed widespread cystic degeneration of the basal cells (Fig. 2*a*, *b*). Other parts of the eye were essentially normal.

Antibody labelling studies by an immunoperoxidase technique described by Taylor and Burns (1974) showed immunoglobulin in the intercellular spaces of the acanthotic conjunctival epithelium and also between individual epithelial cells of the cornea (Fig. 3*a*, *b*). The antibody belonged principally to the IgG class, although weak staining was also achieved with a peroxidase-labelled antiserum to IgM. There was no antibody staining in the non-pigmented epithelium of the ciliary body.

CASE 2

A 65-year-old man had had several myocardial infarcts and had been taking practolol regularly for over three years. After two and a half years on the drug he developed bilateral conjunctival irritation and subsequently was admitted to hospital with malaise and a psoriasiform skin rash. The ocular lesions progressed to cause filamentary keratitis with extensive conjunctival scarring and obliteration of the fornices. There was a complete absence of tear flow and six months later he developed corneal abrasions with severe ulceration which, on the left side, went on to perforate. At this juncture practolol administration was stopped but, although the skin rash resolved, the eye lesions did not improve. Six months after the drug had been withdrawn the patient died.

Histopathology

The right eye was removed post mortem and showed extreme corneal thinning with the formation of a Descemetocoele. In this area there was gross stromal lysis with moderate lymphocytic and vascular invasion.

Address for reprints: P. Wright, FRCS, Consultant Surgeon, Moorfields Eye Hospital, City Road, London EC1V 2PD

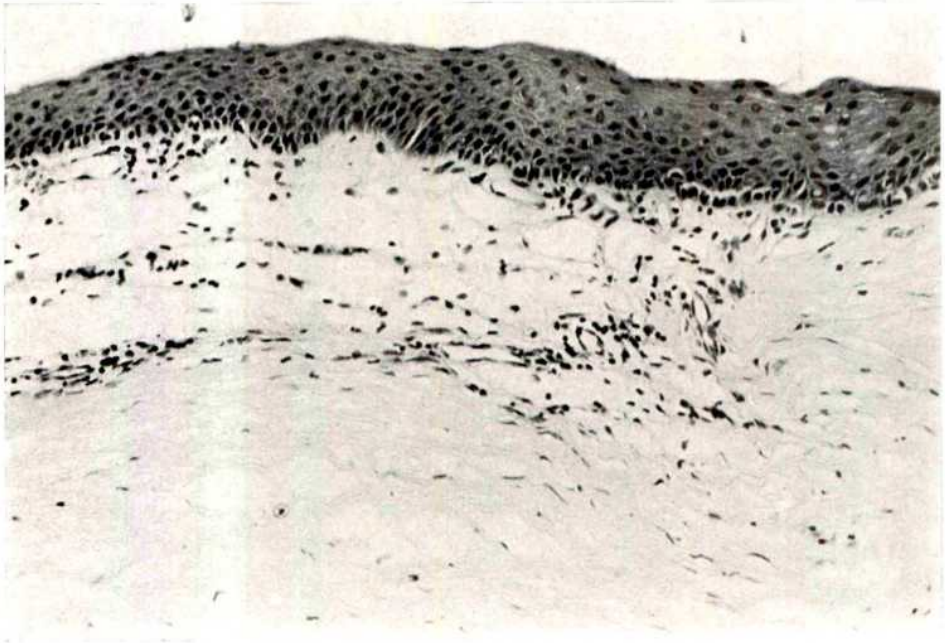

FIG. 1 *Case 1. Section of bulbar conjunctiva showing acanthotic thickening of epithelium with loss of goblet cells and mild lymphocytic infiltration of underlying collagenous stroma. Haematoxylin and eosin.* × 185

Towards the limbus there was again marked inflammation with the formation of granulation tissue, fibrinous exudation, and loss of much of the covering epithelium (Fig. 4). The bulbar conjunctiva was similarly inflamed with such epithelium as remained showing acanthosis and loss of goblet cells. Antibodies of both IgG and IgM classes were demonstrable between individual epithelial cells using peroxidase-conjugated antisera. A mild non-granulomatous iridocyclitis was also present together with some patchy degeneration of the retinal pigment epithelium. Other changes could be ascribed to post-mortem autolysis. Examination of the conjunctiva from the left eye also showed an intense inflammatory reaction with desquamation of all but the basal layer of epithelium. Goblet cells were absent.

The lacrimal gland showed massive fibro-fatty replacement of the parenchyma with a moderate degree of lymphocytic and plasma cell infiltration (Fig. 5). Only a few scattered islands of ductal epithelium remained and there was no sign of secretory tissue. Immunoperoxidase-labelled antibody staining showed immunoglobulin within the plasma cells, but its presence around residual glandular elements was equivocal because of artefacts caused by post-mortem diffusion. Samples of peritoneum, pleura, and pericardium were also examined and found to be very lightly infiltrated with lymphocytes with mild to moderate degrees of fibrous thickening.

CASE 3

A 72-year-old woman, who was confused, deaf, and a poor historian, developed a skin rash, dry eyes, conjunctival scarring, breakdown of the corneal epithelium, and gradual loss of corneal stroma after taking practolol regularly for several years. She had also had several episodes suggestive of small-bowel obstruction due to sclerosing peritonitis, and she eventually died from cardiac failure.

Histopathology

A biopsy of the conjunctiva seven months before death showed mild lymphocytic infiltration of the stroma and IgG/IgM antibody between the cytoplasmic membranes of the overlying squamous epithelium. The epithelium was slightly acanthotic with increased stratification and there was complete absence of goblet cells.

Examination of the eyes post mortem showed much epithelial and stromal ulceration of the central cornea with leucocytic infiltration and vascularization of the surrounding tissue. Residual corneal epithelium at the edges of the ulcers was mildly dysplastic (Fig. 6) and the acanthotic epithelium of the conjunctiva included foci of cystic degeneration. Both eyes also showed moderately severe non-granulomatous iridocyclitis, while immunoperoxidase staining not only confirmed the presence of antibody in the epithelial surfaces of the conjunctivae and corneae but also showed immunoglobulin within the lens epithelium.

Changes in other tissues included varying degrees of fibrous thickening of the pleural, pericardial, and peritoneal surfaces associated with diffuse lymphocytic infiltration (Fig. 7). No lacrimal gland tissue could be found but the parotid, submandibular, and minor salivary gland elements of the buccal mucosa showed only trivial foci of lymphocytic infiltration and no apparent tissue damage. Also, although antibody could be demonstrated in the intercellular spaces of the squamous epithelium of the buccal mucosa, tongue, oesophagus, and skin, there were no associated tissue changes.

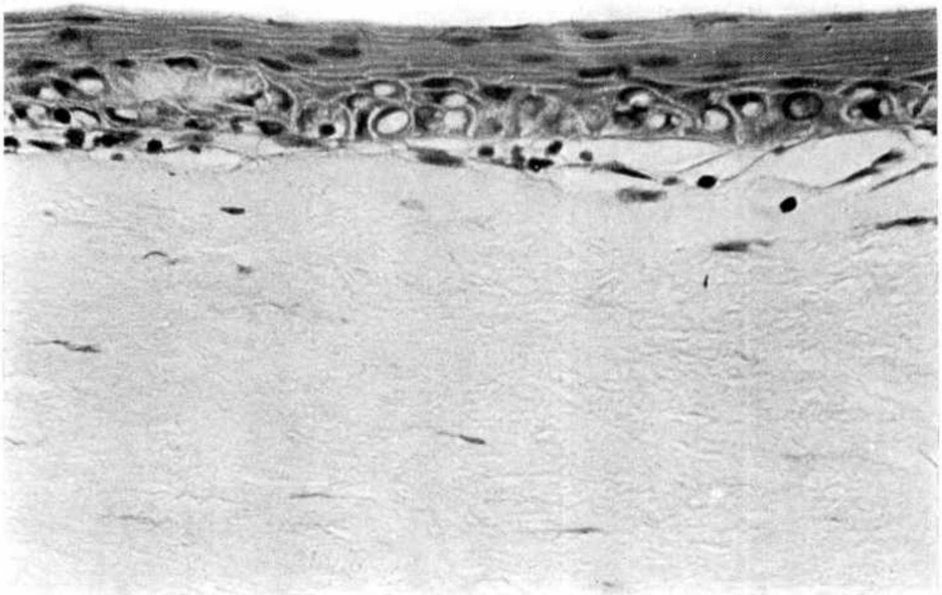

FIG. 2a *Case 1. Basal layers of corneal epithelium show cystic degeneration and there is a little subepithelial vascular ingrowth*

Decalcified sections of the inner ear showed neither antibody fixation nor epithelial abnormality.

CASE 4

A 65-year-old man, who had been taking practolol regularly for two years presented with iritis and increased intraocular pressure. Two months later he developed a marginal corneal ulcer in the right eye which failed to respond to carbolization and treatment with cysteine and steroids. Consequently a tarsorrhaphy was performed, but even this did not prevent the ulcer progressing to create a small perforation. The ocular tension continued to be raised and rather less than one year after ocular lesions first developed the right eye had to be enucleated.

Histopathology

There was marked vascular congestion and leucocytic

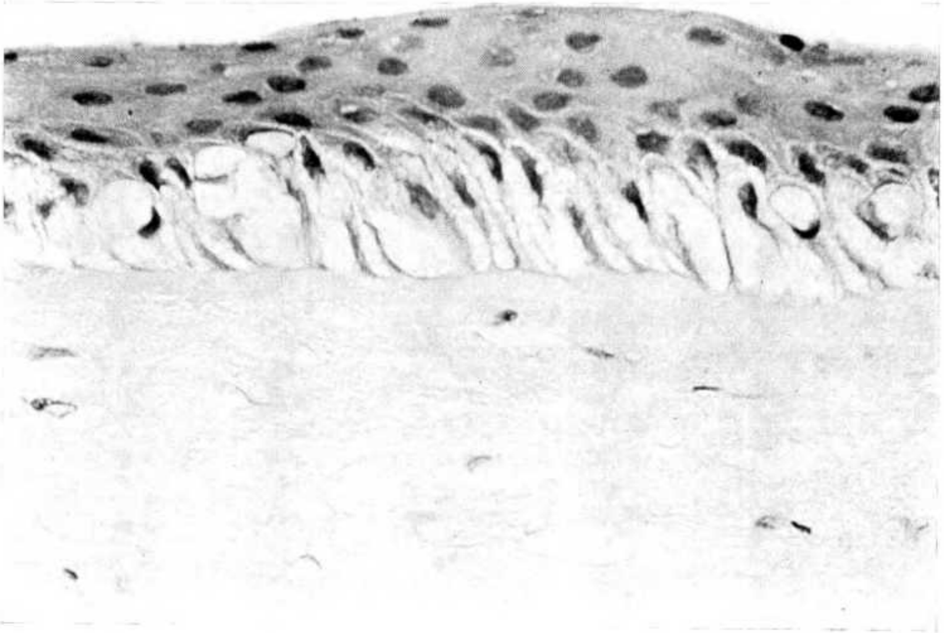

FIG. 2b *Another part of the same cornea showing intense basal cell oedema and cystic degeneration. Haematoxylin and eosin.* ×455

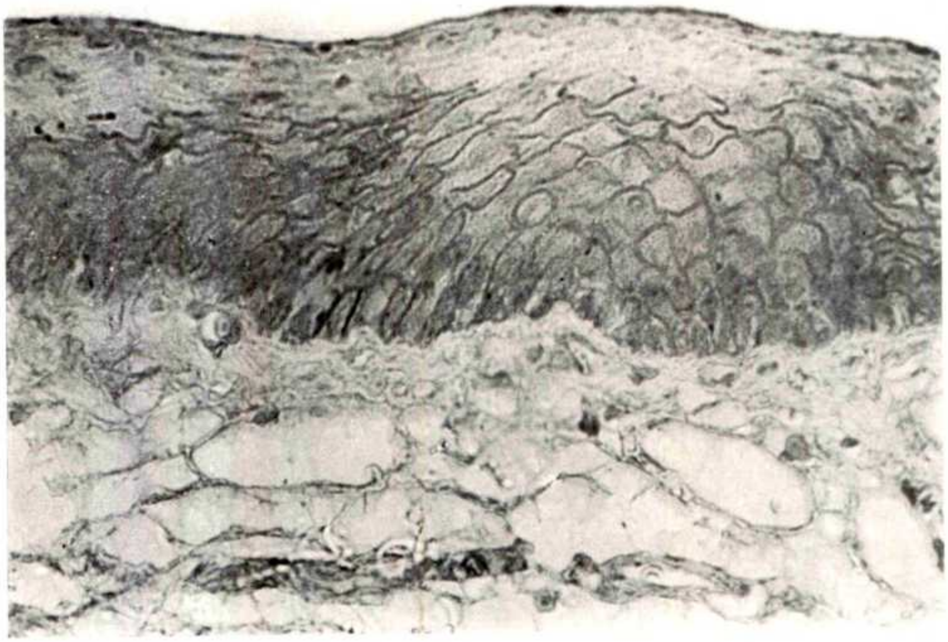

FIG. 3a *Case 1. Immunoperoxidase labelling of antibody located in the intercellular spaces of the acanthotic cells of the conjunctival epithelium.* ×455

infiltration of the bulbar conjunctiva associated with acanthosis of the overlying epithelium, loss of goblet cells, and considerable subepithelial fibrous tissue proliferation. The epithelium of the cornea showed cystic degeneration and absence of Bowman's membrane over a wide area with vascularization of the peripheral stroma. There was also deep stromal ulceration between the centre of the cornea and the inferior limbus with a small perforation. The iris was partially bound to the margins of the perforation and back of the cornea and there was a moderate degree of chronic iridocyclitis. The lens was cataractous with anterior subcapsular fibrosis related to the formation of posterior synechiae: rupture of the lens capsule was also seen. No significant abnormality was seen in the posterior segment of the globe.

Immunoperoxidase studies showed the presence of

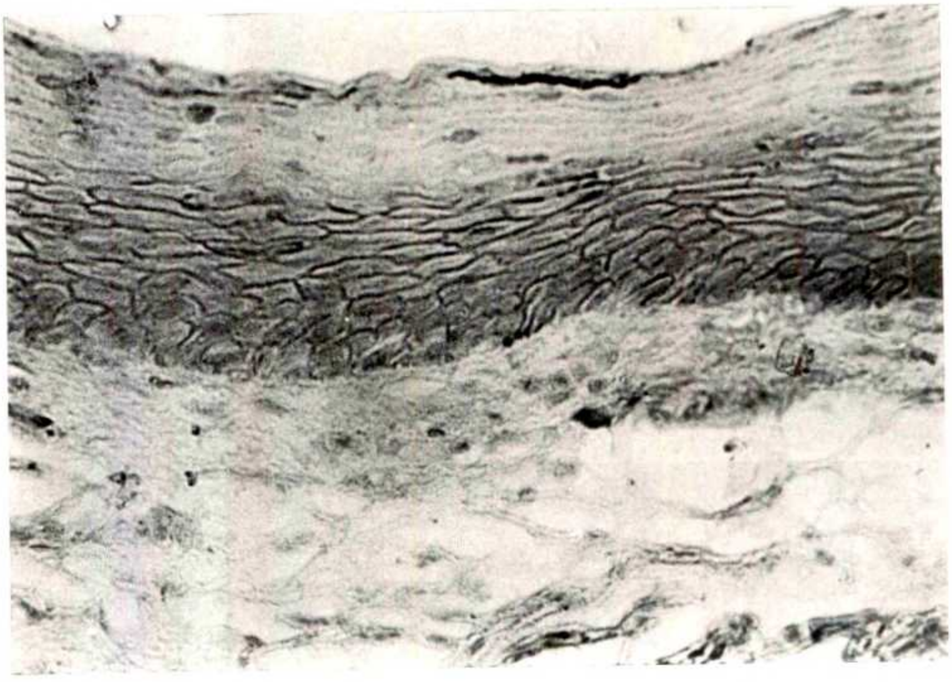

FIG. 3b *Similar preparation showing predominance of antibody fixation in the basal and prickle cell layers.* ×455

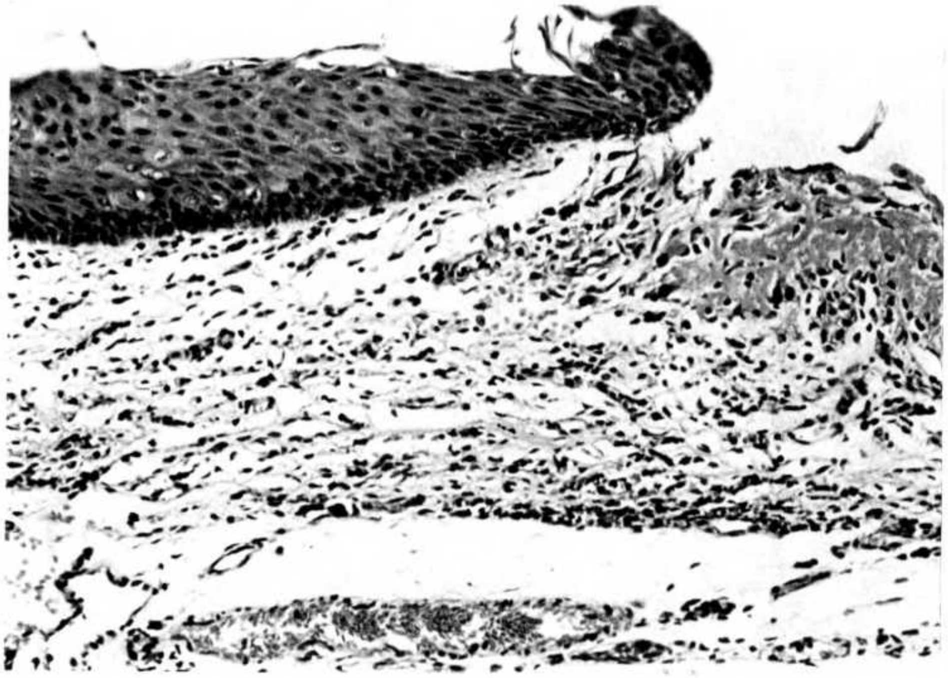

FIG. 4 *Case 2. Section of enucleated eye showing edge of deep corneal ulcer. Residual epithelium is acanthotic and there is much lymphocytic infiltration of underlying collagenous lamellae. Haematoxylin and eosin.* × 185

weak but unequivocal IgG antibody between the cells of the conjunctival and corneal epithelium.

CASE 5

A 65-year-old woman, with angina following myocardial infarction, was treated with practolol for four years. She developed hyperkeratotic skin lesions after one year and her eyes became sore after three years on the drug. Reduced tear flow with subconjunctival fibrosis developed leading to large, persistent epithelial erosions and rapidly maturing cataracts. The left cornea was covered with a conjunctival flap after intracapsular

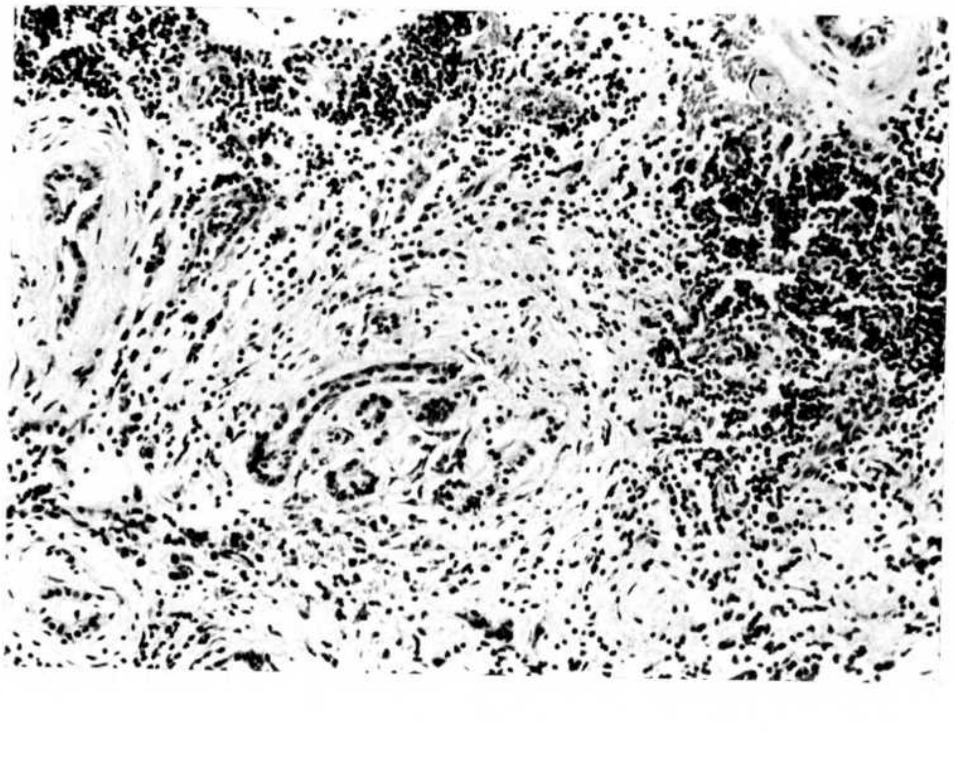

FIG. 5 *Case 2. Section showing lymphocytic and plasma cell infiltration of lacrimal gland associated with replacement of secretory acini by fibrous tissue. Only scattered collecting ductules remain. Haematoxylin and eosin.* × 185

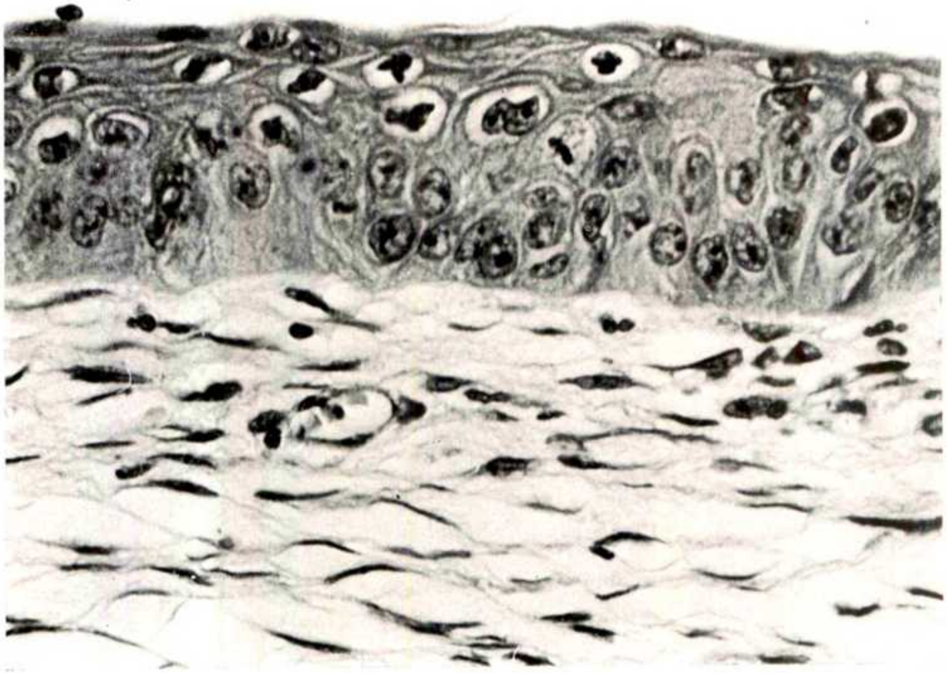

FIG. 6 *Case 3. Normal regular arrangement of corneal epithelium is disturbed and degenerate cells present in superficial layers. Bowman's membrane has been destroyed and there is fibrovascular proliferation beneath epithelium. Haematoxylin and eosin.* × 455

removal of the cataract. The right eye was managed with a soft contact lens.

Histopathology

Biopsy of the conjunctiva of the right eye showed marked acanthosis and spongiosis of the epithelium with absence of goblet cells and pronounced chronic inflammation of the underlying stroma (Fig. 8). There was also polymorphonuclear leucocytic infiltration of the epithelium but immunoperoxidase studies showed only weak antibody fixation in the intercellular spaces. Subsequently examination of the lens and a portion of iris from the left eye showed cataractous lens changes and mild iritis. Immunoglobulin, as revealed by immunoperoxidase-labelled antibody, was present beneath the capsule of the lens and in the iris stroma. In neither structure, however, was there any evidence of complement (C'_3) fixation.

Electron microscopy

There was no apparent cellular abnormality in the conjunctival epithelium apart from the absence of goblet cells and the presence of polymorphonuclear leucocytes (Figs 9, 10). The cytoplasmic membranes of individual squamous cells were intact, the desmosomal junctions in particular being normally formed and undisturbed. Similarly the hemidesmosomal junctions between the basal epithelium and the basement membrane appeared to be healthy (Fig. 11).

CASE 6

A 57-year-old man, with widespread arterial disease and hypertension, was treated with practolol for two and a half years. At the end of two years he had developed hyperkeratosis of his hands and a generalized psoriasiform skin eruption. The eyes became sore shortly afterwards with dryness, subconjunctival fibrosis, large persistent epithelial erosions of the corneae, and rapidly maturing cataract. Both eyes were treated with large doses of corticosteroids, while the left cornea was covered with a conjunctival flap and an intracapsular cataract extraction was carried out. He subsequently had several episodes of small-bowel obstruction due to fibrosing peritonitis, but these settled on conservative treatment.

Histopathology

Limited scrapings of the corneal epithelium of the right eye failed to show any morphological abnormality, although immunoperoxidase staining showed the presence of IgG antibody and the C'_3 component of complement between individual epithelial cells. Examination of the conjunctiva four months later showed an acanthotic epithelium devoid of goblet cells. Immediately beneath the epithelium there was considerable plasma cell and lymphocytic infiltration associated with reactive fibrosis. Immunoperoxidase studies of unfixed and washed tissue confirmed the presence of IgG/IgM antibody in the interepithelial spaces, but staining for complement (C'_3) was entirely negative.

Discussion

The conjunctival lesions associated with prolonged practolol administration take the form of thickening and acanthosis of the epithelium with loss of goblet

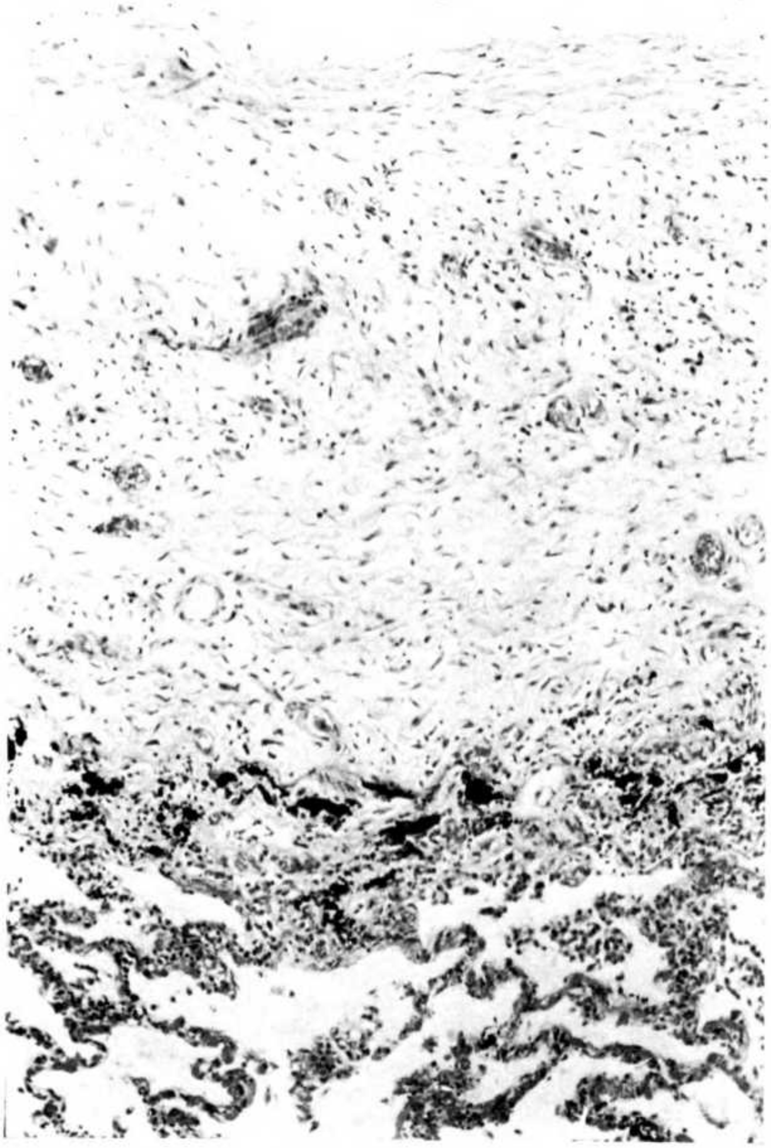

FIG. 7 *Case 3. Section of lung showing marked fibrous thickening of the overlying plasma. Scanty lymphocytes also present. Haematoxylin and eosin.* × 230

cells and chronic inflammatory changes leading to fibrosis in the underlying stroma. The corneal epithelium appears to be less obviously affected but may show cystic degeneration, while in two of the present cases there was pronounced epithelial and stromal ulceration progressing to perforation. Stromal or subepithelial vascularization was a feature of corneae showing epitheliopathy and ulceration. In part it is probably appropriate to attribute the epidermalization of the conjunctival epithelium to inadequate flow of tears, since dryness of the eye is a constant clinical finding in patients with ocular lesions (Wright, 1974; 1975). In neither of the two cases examined post mortem could any functional lacrimal gland tissue be found. The absence of secretory IgA in the limited tear secretion (Wright, 1975; Rahi and Garner, in press) also emphasizes the failure of lacrimal gland function. Nevertheless, xerophthalmia alone is not usually associated with the measure of subepithelial fibrosis seen in the conjunctivae of eyes damaged by practolol, which suggests that the lesion might represent a combination of deficient tear flow and a primary change in the tissues of the conjunctiva. Disappearance of goblet cells, which was noted in all specimens, would probably

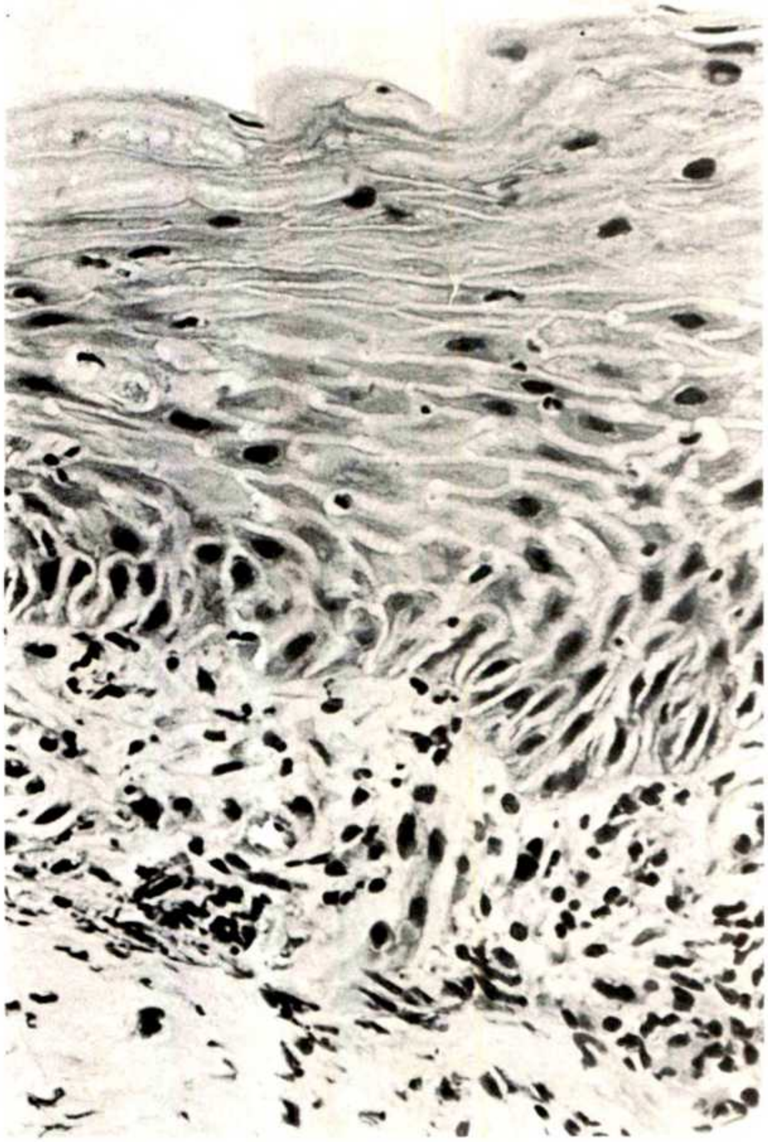

FIG. 8 *Case 5. Spongiosis of acanthotic conjunctival epithelium associated with presence of lymphocytes, plasma cells, and proliferating fibroblasts in underlying stroma. Haematoxylin and eosin.* ×455

contribute to the epithelial changes in the cornea since the mucus secretion of the conjunctiva is intimately concerned with the maintenance of corneal hydration (Lemp, Dohlman, Kuwabara, Holly, and Carroll, 1971; Dohlman, 1971). The immediate cause of the goblet cell loss is not clear but the parallel with pemphigus, benign mucous membrane pemphigoid, and Stevens-Johnson syndrome suggests that it is related to degenerative and reactive changes in the squamous epithelium. Similarly, although ulceration of the cornea is likely to be facilitated by xerosis, it is also possible that intrinsic changes in the corneal epithelium are involved, spongiosis and intraepithelial cyst formation, comparable to that observed as a result of practolol medication, having been recorded in a variety of corneal conditions in which there is defective epithelium (Tripathi and Bron, 1973). Necrosis, or 'melting' of the corneal stroma, might be a further index of an abnormal epithelium (Slansky and Dohlman, 1970).

As yet, however, the cause of the intrinsic epithelial defect is uncertain. The finding of the immunoglobulin between individual epithelial cells is reminiscent of pemphigus, in which similarly located antibodies have been described. In pem-

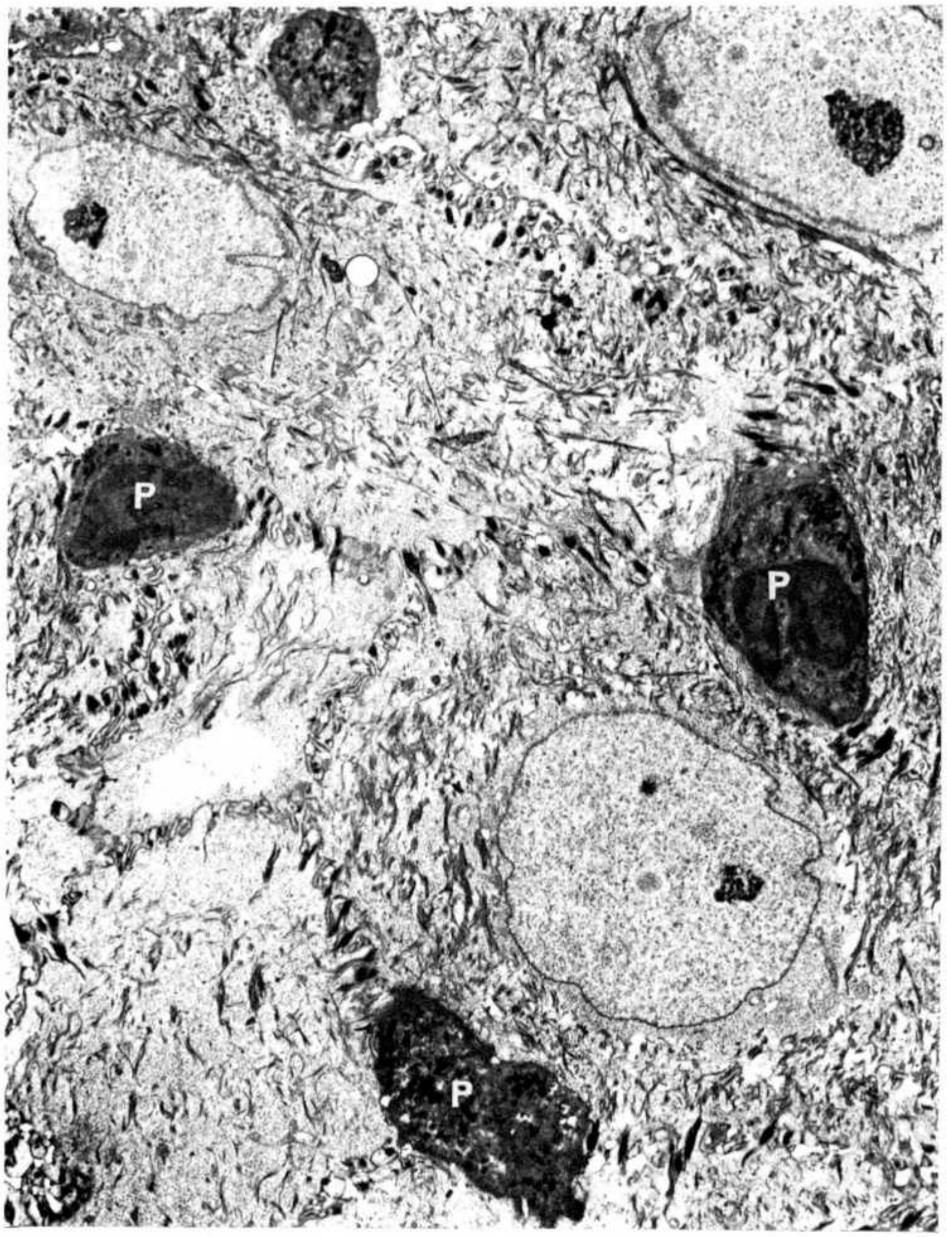

FIG. 9 *Case 5. Electron micrograph of acanthotic squamous cells in conjunctiva showing intact intercellular junctions. Scattered polymorphonuclear leucocytes (P) are present in intercellular spaces.* ×4000

phigus the antibody appears to be directed against the intercellular desmosomal attachments and exacerbations of the disease are commonly preceded by a rise in antibody titre (Sams and Jordan, 1971), while repeated injections of antiserum directly into the skin of monkeys have been claimed to provoke acantholysis (Beutner, 1973). On the other hand, some workers (Amos and others, 1975) consider the reported evidence for the toxic properties of pemphigus antibodies to be unconvincing and suggest that the antibody could be merely a cytophilic immunoglobulin which attaches in a non-specific manner to squamous epithelium. Apart from analogous uncertainties, the autoantibodies associated with practolol toxicity differ from those in pemphigus in combining with a component of the intercellular space which is removed by trypsin digestion, whereas the affinity of pemphigus antibody for epidermal cell membranes is not affected by trypsinization (Amos and others, 1975). Moreover, bullous skin eruptions comparable to pemphigus are not a feature of the

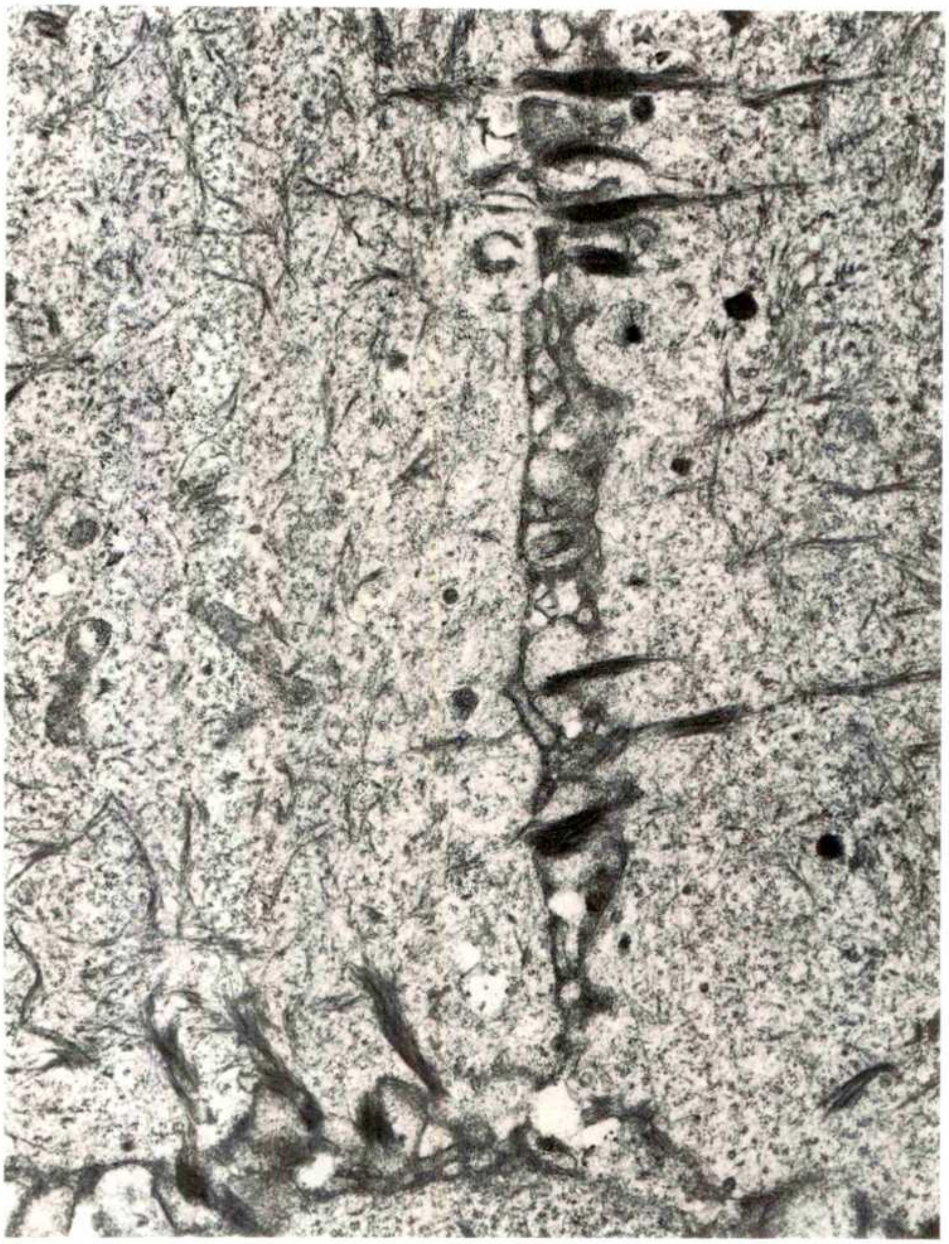

FIG. 10 *Case 5. Electron micrograph showing normal complement of intact desmosomal junctions between cells of conjunctival epithelium.* ×16 500

rash associated with practolol administration (Felix and others, 1974; Wright, 1975). In addition, despite our finding that fixation of immunoglobulin to epithelial cell membranes was present in unfixed tissue subjected to prolonged washing, and thus unlikely to be an artefact due to non-specific fixation of protein diffusing from the adjacent blood vessels, we were unable to demonstrate complement fixation in such tissue. This suggests that *in-vivo* activation of complement does not occur and that, consequently, the antibodies are probably not cytotoxic. In which case the formation of autoantibodies in patients with practolol-induced ocular disease is more likely to be secondary to epithelial damage than its cause, although the possibility that the effect of the lymphoid response was impeded by topical corticosteroid application should not be overlooked.

The cause of the lacrimal gland damage is also uncertain. The presence of antinuclear factor, the evidence of reduced salivary secretion in many, the report of joint pain in occasional patients

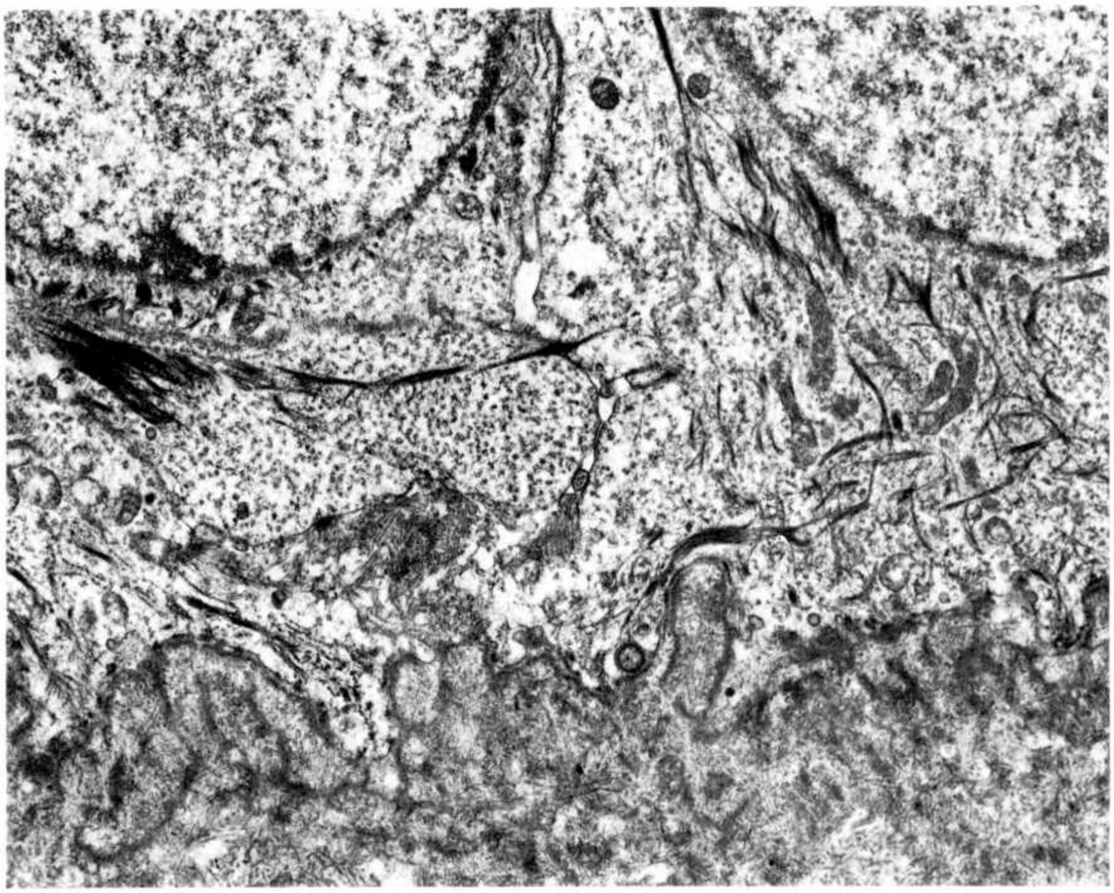

FIG. 11 *Case 5. Electron micrograph of junction between basal epithelium and its basement membrane showing absence of any structural abnormality.* × 12 500

(Raftery and Denman, 1973), and the histological evidence of lymphocytic infiltration of the gland are superficially suggestive of a Sjögrenoid lesion. Alternatively, in contrast to a predominantly immunological reaction it may be that direct drug-induced toxicity is responsible (Wright, 1975). But here again, although experiments in laboratory animals indicate that practolol is prone to accumulate in the lacrimal gland parenchyma, the drug appears to be well tolerated by these animals, neither immune response nor lacrimal damage accruing.

Because the incidence of oculodermal toxicity in patients receiving practolol is of a quite low order it is probable that an individual idiosyncrasy, possibly genetically determined, is involved.

Of the two cases in which the lens was studied one was cataractous and both showed some fixation of antibody in the subcapsular epithelial region. The absence of detectable complement fixation, however, suggests that the uptake was possibly non-specific and probably inconsequential.

The finding of fibrous thickening of the peritoneum, pleura, and pericardium in cases 2 and 3 is analogous to the serosal lesions described by Windsor, Kurrein, and Dyer (1975), although in our cases the degree of thickening was insufficient to produce such intractable abdominal symptoms as those described in other reports (Brown and others, 1974; Meyboom, 1975; Windsor and others, 1975).

Summary

The ocular side-effects of prolonged practolol administration concern the cornea and conjunctiva and are related to deficient tear secretion and the formation of an autoantibody which has an affinity for the intercellular zones of squamous epithelium. Histopathological study of six cases, including a review of the necropsy findings in two, showed destruction of lacrimal gland tissue, epidermalization of the conjunctival epithelium, with epithe-

liolysis and stromal ulceration of the cornea leading to perforation in two patients. Immunoperoxidase studies showed fixation of specific antibody in the corneal and conjunctival epithelium but, in the one case in which the tissue could be adequately studied, complement fixation could not be demonstrated. Possibly, therefore, the immune response in patients with practolol-induced ocular damage is secondary to the epithelial disturbance rather than its cause.

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Ageing and degeneration in the macular region: a clinico-pathological study

S. H. SARKS
Lidcombe Hospital, Sydney, Australia

Certain changes at the macula can be attributed to normal ageing. Metabolic waste accumulates in the cells of the retinal pigment epithelium. Connective tissue, especially altered collagenous fibres, increases in Bruch's membrane, and vascular changes inherent in the vessels themselves can be shown in the choroid. Which of these ageing processes is implicated in the pathogenesis of senile macular degeneration or at what stage they become pathological is uncertain. Most cases of senile macular degeneration are believed to be due to sclerosis and obliteration of the choriocapillaris in the central area (Duke-Elder, 1966), while electron microscopic studies by Hogan (1967, 1972) emphasized the role of ageing changes in Bruch's membrane and the retinal pigment epithelium.

Senile macular degeneration shows a wide spectrum of clinical appearances, reflecting the different anatomical levels predominantly affected at the time. Thus the fundus may present a disturbance of retinal pigmentation, exposure and abnormality of the choroidal vessels, drusen of various appearances, evidence of exudation, haemorrhage or neovascularization from the choroid, and intraretinal and preretinal changes. This has resulted in the recognition of many distinct and generally unrelated entities since the disease was originally described by Haab (1885). The most significant advance in recent years stems from the original demonstration by Verhoeff and Grossman (1937) that senile disciform degeneration results from the organization of haemorrhage beneath the retinal pigment epithelium. The cause of this haemorrhage was investigated by subsequent observers, notably by Maumenee (1965), and by Gass (1967), who formulated our current knowledge of the predisciform state when he proposed that neovascularization from the choroid may occur in response to the accumulation of abnormal deposits beneath the pigment epithelium and that this may precede haemorrhage.

Current interest therefore centres on the recognition of the predisciform state and the use of photocoagulation to prevent the complications of subretinal neovascularization. A definitive form of treatment has thus been evolved, although applicable to only a limited number of patients suffering from an advanced degree of degeneration. Further, it has been difficult to rationalize and to evaluate this treatment because the natural history of the disease remains poorly understood (Gass, 1973). Not surprisingly, therefore, the majority of ophthalmologists regard degenerative disease of the retina and the macula as the most difficult to treat and the most in need of research (Hammond and Spalter, 1973).

The present investigation reports the results of clinical and pathological examination of 378 eyes. The aim of this study was to identify the age-related changes in the retinal pigment epithelium, Bruch's membrane, and choriocapillaris which could be regarded as normal and to relate the progression of these changes to the evolution of senile macular degeneration.

Material and methods

Histological examination was performed on 378 eyes in which the macula had presented a variety of clinical appearances ranging from normal to the late manifestations of senile macular degeneration. This series did not include eyes suffering from degenerative myopia, retinal vascular disease affecting vision, advanced simple glaucoma, or eyes in which an adequate view of the macula had not been obtained clinically. The 378 eyes were collected during the period 1966–75 from 216 patients, 199 men and 17 women, whose ages ranged from 43 to 97 years. All patients had been admitted to Lidcombe Hospital, generally for long-term care, and a full ocular examination was performed at intervals. Fundus photographs were taken whenever possible and selected patients were submitted to fluorescein angiography. The average interval between the last clinical examination and the time of death was 16·4 months.

When eyes became available after death they were fixed in Lillie's buffered formalin. They were opened in the horizontal plane and examined macroscopically. The position on the sclera corresponding to the macula was localized by observing the tip of a fine probe during transillumination, and the spot was marked with con-

Address for reprints: S. H. Sarks, Lidcombe Hospital, Sydney, Australia

centrated Harris's haematoxylin solution. The eyes were then double embedded (Tait Smith, 1976). Serial sections 8 μm thick were cut horizontally through the disc and the macula. Every tenth section was stained by the picro-Mallory method as modified by Lendrum, Fraser, Slidders, and Henderson (1962) and examined histologically. This stain was selected for routine use as it distinguishes fibrin (red), collagen (blue), and neural tissue (pink). In areas of interest the intervening sections were examined after staining with the following: haematoxylin and eosin, luxol fast blue, periodic acid-Schiff, Verhoeff's elastic stain, chloranilic acid, Wilder's silver stain, Mallory's PTAH, and congo red.

Results

Histological changes associated with ageing were detected at the level of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris before clinical abnormality became apparent. Subsequent changes in these tissues also correlated closely with the clinical progress of senile macular degeneration. In the present investigation the ageing and degenerative changes at the macula were therefore classified according to the histology.

The age-related changes in Bruch's membrane comprised thickening, hyalinization, patchy basophilia, and precipitation of calcium crystals with chloranilic acid. These changes were first seen beneath the macula and adjacent to the disc and remained most advanced in these regions. An arbitrary assessment of the findings was made in sections beneath the fovea. The thickness of a representative segment of the membrane was compared to the vertical diameter of the underlying choroidal capillary. The thickness was then expressed according to whether Bruch's membrane: choriocapillaris was one-quarter or thinner, one-third, or one-half or thicker (Fig. 1).

Hyalinization of the membrane was indicated by increased periodic acid-Schiff positivity and a change from blue to red staining with the picro-Mallory method. The extent was noted to the nearest half disc diameter and four grades were recognized. Grade 1 referred to small patches which appeared in the fifth decade and later became continuous. Grade 2 hyalinization extended into the intercapillary pillars (Fig. 2) and grade 3 hyalinization reached the level of the outer surface of the choriocapillaris (Fig. 3). Hyalinization completely surrounding several choroidal capillaries was occasionally observed (grade 4).

Two types of drusen were noted on Bruch's membrane. Some deposits were hyalinized and globular in shape, others were dome-shaped and had a granular structure. These drusen could also be distinguished on clinical examination, the former appearing round and discrete while the latter showed greater variation in size and shape with ill-defined outlines.

The earliest light microscopic evidence of disturbance to the pigment epithelium was associated with the appearance of a finely granular deposit at the base of the cells. This material was eosinophilic, was unstained with luxol fast blue, was only moderately positive to periodic acid-Schiff, but stained blue with the picro-Mallory method. The formation of this basal linear deposit beneath the macula proved the most reliable histological criterion of the stage of the disease and correlated most closely with the clinical findings, although this was influenced to some extent by the time interval between clinical and histological examinations.

HISTOLOGICAL GROUPS

The eyes were divided into six groups according to the degree of histological abnormality (Fig. 4). The first four groups reflected the progressive development of the basal linear deposit and the visual acuity recorded in these eyes is shown in Table I. Groups V and VI represented the late stages of geographical atrophy and disciform

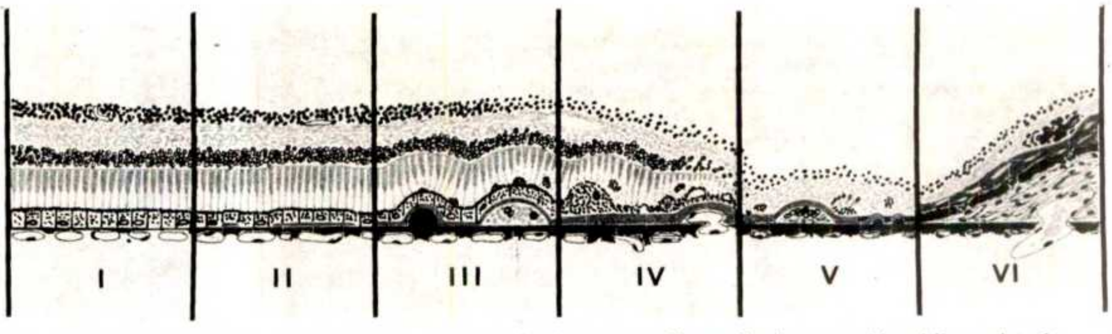


FIG. 4 *Diagram illustrating histological classification of 378 eyes according to development of basal linear deposit under retinal pigment epithelium*

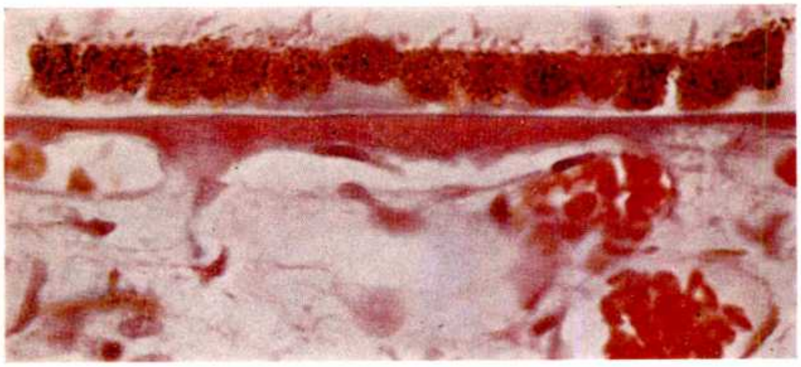


FIG. 1 *Example of Group II. Section passing through macular region of patient aged 86 with normal fundus and 6/12 vision. Marked thickening of Bruch's membrane encroaching on choroidal capillary, ratio thickness membrane : capillary lumen almost 1:1. Localized deposit of blue staining finely granular material related to thickened membrane. Picro-Mallory.* ×500

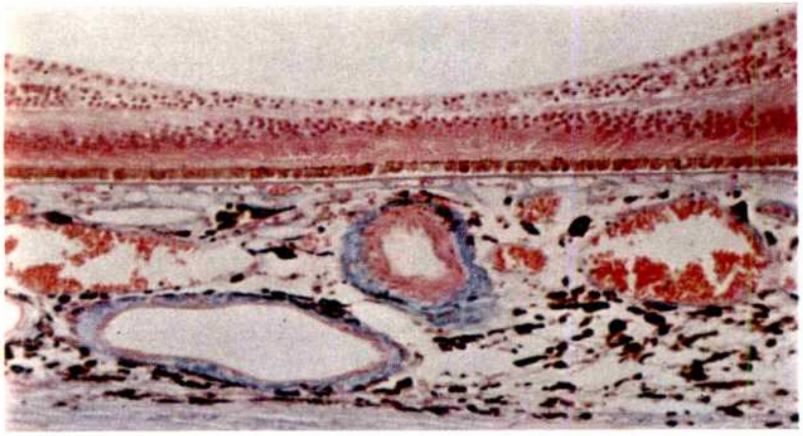


FIG. 2 *Example of Group I. Section through normal macula of left eye of patient whose right fundus is illustrated in Fig. 5. Bruch's membrane shows grade 2 hyalinization and there is no evidence of basal material under retinal pigment epithelium. The pigmented choroid is of normal thickness and vessels are normal. Picro-Mallory.* ×150

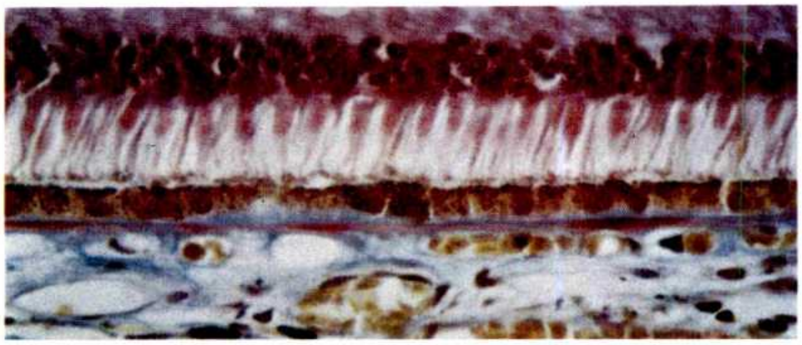


FIG. 6 *Example of Group II. Section through paramacular area of left eye of 72-year-old man with 6/6 vision and normal fundus. Beneath retinal pigment epithelium localized deposits of finely granular material are related to deeply staining segments of Bruch's membrane. These segments were basophilic with haematoxylin and eosin stain. Picro-Mallory.* ×500

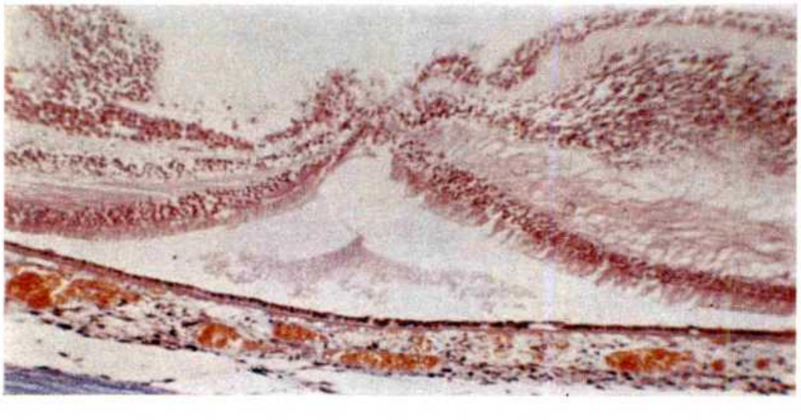


FIG. 7 *Example of Group III. Section through macula of 79-year-old man whose fundus had appeared normal with 6/9 vision. Basal linear deposit now forms thin continuous layer and Bruch's membrane shows widespread grade 3 hyalinization extending into the intercapillary pillars to the level of outer surface of choriocapillaris. Picro-Mcllory.* ×75

FIG. 3 *Example of Group IV, showing thick basal linear deposit related to grade 3 hyalinization of Bruch's membrane. Section of eye shown in Fig.* 11. *Picro-Mallory.* ×500

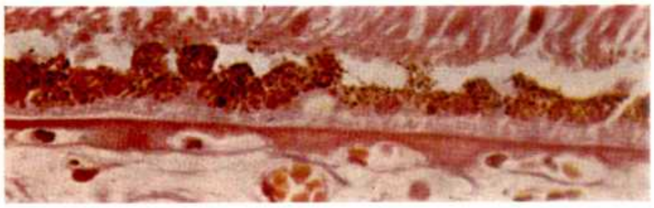


FIG. 8 *Example of Group IV. Section through macula of 83-year-old man whose fundus had shown coarse pigmentary disturbance although vision had remained 6/9. Note thick continuous basal linear deposit and degeneration of overlying pigment epithelium with liberation of pigment-laden cells into subretinal space. Bruch's membrane shows thickening and pillars of grade 3 hyalinization. Picro-Mallory.* × 150

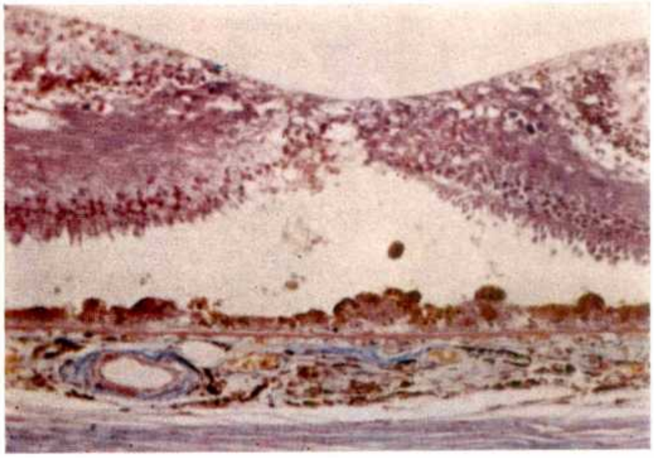


FIG. 17 *Example of Group IV progressing to Group V. Sections passing through macula of eye in Fig.* 16. *Basal linear deposit forms continuous hyalinized and very thickened layer under macula. Pigment epithelium shows marked attenuation and seems about to disappear.*
Top : periodic acid-Schiff. ×45.
Bottom : Picro-Mallory. ×150

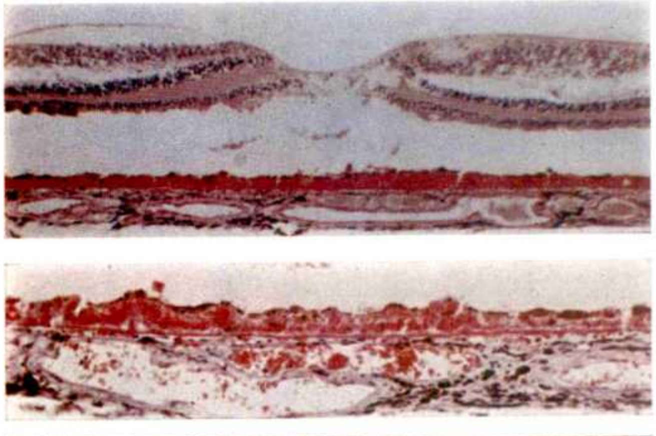
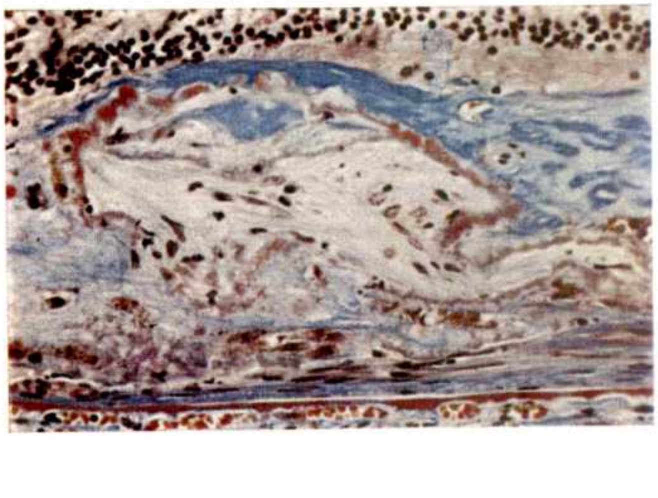


FIG. 22 *Example of Group VI. Section passing through disciform scar in eye of 80-year-old patient. Hyalinized basal linear deposit has been folded into the mass by successive waves of fibrous tissue. Picro-Mallory.* ×300



degeneration in which vision was greatly reduced when the fovea was involved. Table II shows the associated histological and clinical findings, and Table III shows the age distribution of the 216 patients.

Group I (No basal linear deposit)

In this group (120 eyes) there was no trace of the basal linear deposit and the retinal pigment epithelium appeared normal. The average extent of grade 2 hyalinization of Bruch's membrane was 2·0 disc diameters, and even eyes from patients in the 40 to 50 year age group showed some evidence of grade 1 hyalinization. Small drusen of the hyalinized globular variety were noted in 23 eyes but had no detectable effect on vision, although none was located at the fovea.

Table I *Visual acuity recorded in Groups I–IV (333 eyes)*

Visual acuity	*Group I*	*Group II*	*Group III*	*Group IV*
6/6	66 (55·0)	29 (26·1)	6 (10·0)	2 (4·8)
6/9	17 (14·2)	32 (28·9)	23 (38·3)	2 (4·8)
6/12	6 (5·0)	18 (16·2)	12 (20·0)	8 (19·0)
6/18–6/24	4 (3·3)	9 (8·1)	12 (20·0)	17 (40·5)
<6/24	2 (1·7)	1 (0·9)	1 (1·7)	10 (23·8)
Unknown	25 (20·8)	22 (19·8)	6 (10·0)	3 (7·1)
Total	120	111	60	42

Percentages are shown in parentheses

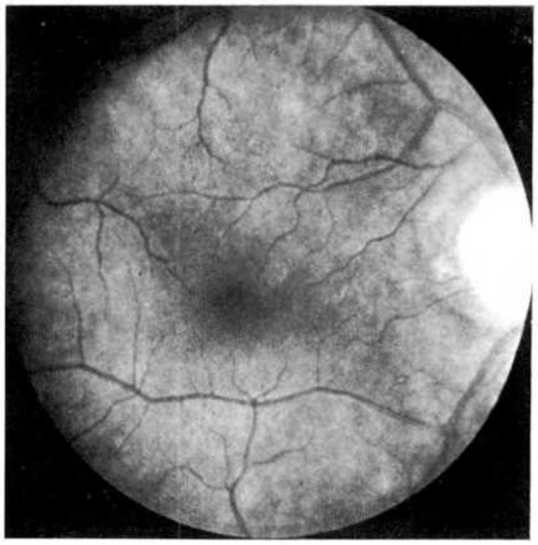


FIG. 5 *Normal right fundus of man aged 67. Left fundus was identical. Vision 6/6 in both eyes*

The average age of patients in this group was 67·5 years and no pigmentary changes were noted on clinical examination. Figs 2 and 5 illustrate these normal findings. 6/6 vision was recorded in

Table II *Clinical and histological findings in 378 eyes, grouped according to appearance of basal linear deposit*

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*	*Group VI*
No. of eyes	120	111	60	42	24	21
Basal linear deposit	Absent	Patchy	Thin continuous	Thick continuous	Persists after loss of pigment	Incorporated into scar
Bruch's membrane/choriocapillaris						
(a) Average limits of hyalinization in disc diameters						
Grade 2	2·0	2·5	3·0	3·9	5·1	5·7
Grade 3	Nil	odd pillars	1·0	3·0	3·7	3·3
(b) $\frac{\text{Thickness of membrane*}}{\text{capillary lumen}}$	$\frac{1}{3{\cdot}7}$	$\frac{1}{3{\cdot}4}$	$\frac{1}{2{\cdot}9}$	$\frac{1}{2{\cdot}3}$	$\frac{1}{2{\cdot}2}$	$\frac{1}{2{\cdot}4}$
Incidence of subretinal neovascularization (percentage)	0	0	0	14·3	41·7	100
Clinical disturbance of pigmentation (percentage)						
Nil	100	96·4	41·6	4·7	Geographic atrophy	Disciform degeneration
Fine	0	3·6	46·7	16·7		
Coarse	0	0	11·7	78·6		
Average age of patients (years)	67·5	75·3	81·9	84·0	85·6	81·9

*Average

Table III *Age distribution of patients according to histological classification of 378 eyes*

Age group	*Group I*		*Group II*	*Group III*	*Group IV*	*Group V*	*Group VI*	*Total*
	Vision 6/6	*Vision < 6/6*						
-59	16	15	2	0	0	0	0	33
60-69	29	7	25	4	0	0	0	65
70-79	21	17	43	14	11	2	7	115
80-89	0	15	38	34	22	20	14	143
90+	0	0	3	8	9	2	0	22
Total	66	54	111	60	42	24	21	378

only 66 of the 120 eyes, and in none of the eyes of patients aged 80 years and over (Table III). In most eyes the lowered visual acuity was ascribed to hazy media or to failure of concentration, but in others no cause was apparent.

Group II (Patchy basal linear deposit)

In this group (111 eyes) the basal linear deposit appeared in patches beneath three to eight retinal pigment cells, which showed slight distortion. The average extent of grade 2 hyalinization of Bruch's membrane was 2·5 disc diameters with occasional pillars of grade 3 hyalinization. Grade 3 hyalinization was associated with widening of some pillars and also with thickening of the membrane, resulting in encroachment on the choriocapillaris. It was at this stage that degenerative changes in the overlying pigment epithelium were first observed (Figs 1, 6). Drusen were present in the macular region in 22 eyes and were predominantly of the hyalinized globular variety.

The average age of patients in this group was 75·5 years and nearly all eyes showed no clinical disturbance of pigmentation (Table II). The most commonly recorded visual acuity was 6/9 (Table I), with an about equal incidence of eyes in which vision was better (26·1 per cent) and worse (25·2 per cent).

Group III (Thin continuous basal linear deposit)

In this group (60 eyes) the linear deposit formed a thin continuous layer under the macula. The average extent of grade 3 hyalinization was 1·0 disc diameter but the deposit sometimes extended more widely, becoming patchy before petering out (Fig. 7). The overlying pigment cells were irregular and the outline of individual cells was less distinct so that they appeared fused together. The rod and cone processes were generally separated from the pigment epithelium at the macula and some appeared stunted. Drusen were present in 25 eyes with an about equal incidence of the hyalinized and granular varieties.

The average age of patients in this group was 81·9 years. The most common visual acuity was again 6/9, but 6/6 vision was recorded in only 10 per cent of the eyes. More than half the eyes showed a clinical disturbance of pigmentation, predominantly a fine clumping of pigment (Table II), and this included 23 of the 25 eyes with histological evidence of drusen. The incidence of fundus abnormality is probably underestimated owing to the interval after the clinical examination.

Group IV (Thick continuous basal linear deposit)

This group (42 eyes) showed thickening of the basal linear deposit, sometimes to about the height of normal pigment epithelium (Fig. 8). Globules of hyalinized material and small foci of calcification were sometimes demonstrated in the material. The pigment epithelium appeared as an attenuated layer in which cell outlines were lost and nuclei were few. In some areas proliferative changes were observed, large pigment-laden cells being shed into the subretinal space, and occasional cells contained hyalinized material or developed cystic changes. Localized mounds of pigment granules were also noted. The photoreceptors, which were sometimes absent over the mounds of pigment granules, showed a greater degree of retraction and distortion in this group. The basal linear deposit attained its maximum thickness over grade 3 hyalinization of Bruch's membrane, the average extent of which was 3·0 disc diameters. The underlying choroidal capillaries were wide-spaced and often narrowed, so that the average ratio of membrane thickness to capillary lumen was almost 1:2. This was due not only to encroachment by the thickened membrane but also to reduction of the capillary lumen by surrounding fibrous tissue. Drusen were present in 15 eyes. They were mainly of the granular type and several were undergoing calcification.

Six of the 42 eyes (14·3 per cent) showed thin

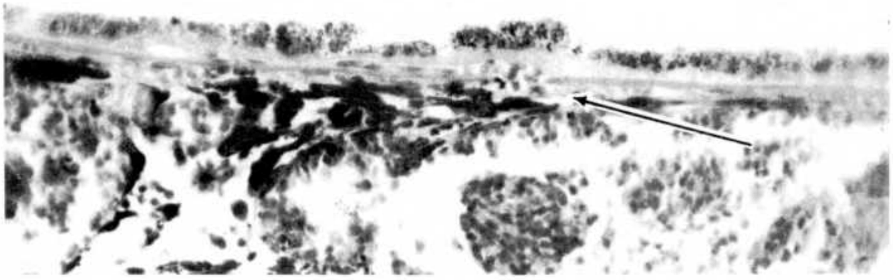


FIG. 9 *Section through macular area of 72-year-old man whose fundus had shown coarse pigmentary disturbance, vision 6/18. Capillary (arrow) passes through small gap in Bruch's membrane to invade basal linear deposit. Picro-Mallory.* × 300

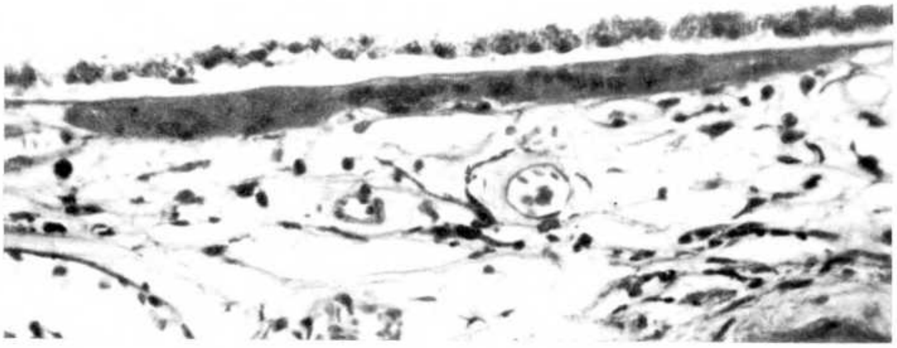


FIG. 10 *Section showing giant cell beneath thinned segment of Bruch's membrane in eye from 77-year-old man. There were several areas of fibrovascular invasion but serial sections did not show break in Bruch's membrane at site of giant cell. Picro-Mallory.* × 500

capillary membranes passing through gaps in Bruch's membrane and spreading beneath the retinal pigment epithelium in the macular region for up to half a disc diameter. Drusen were a conspicuous feature in two of these eyes but were not immediately related to the breaks in the membrane, the capillaries invading the basal linear deposit (Fig. 9). Giant cells were often prominent near the gaps in the membrane but were also found in relation to thinned segments of the membrane where serial sections did not show a break in the immediate vicinity (Fig. 10).

The average age of patients in this group was 84 years and the youngest was aged 70. The most commonly recorded visual acuity was 6/24 and almost all eyes showed a clinical disturbance of pigmentation which was predominantly coarse. Fig. 11 shows the tigroid fundus of a 90-year-old man with fine pigmentary changes and 6/9 vision. The basal linear deposit was widespread under the macula (Figs 12, 13) and was appreciably thickened over grade 3 hyalinization (Fig. 3). An electron microscopic section was taken from the paraffin block in this area. This technique is unsatisfactory for fine detail but shows the thick deposit lying on Bruch's membrane (Fig. 14). The hyalinized membrane and the intercapillary pillars contain irregular-banded collagen, vesicles, and tube-like structures. The electron micrograph (Fig. 15) represents the macular region of a man aged 71 who showed coarse pigmentary mottling in both eyes, and histological examination of the fellow eye showed a thick layer of basal material. The deposit contains banded material lying between the plasma infoldings of the retinal pigment epithelium and the basement membrane.

Fig. 16 shows the tigroid fundus of an 80-year-

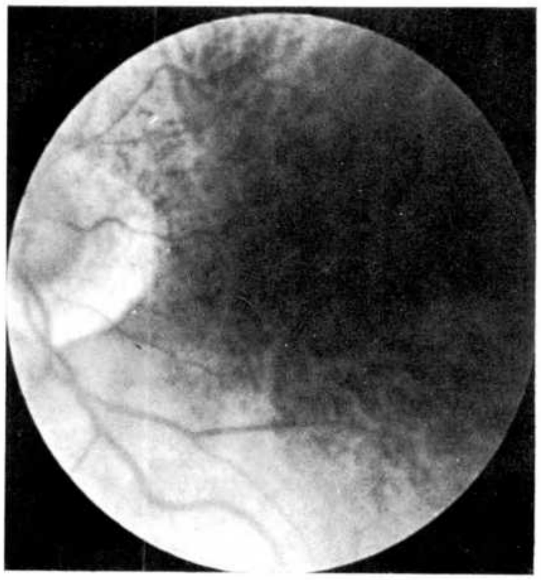


FIG. 11 *Tigroid fundus of 90-year-old man. Macula showed fine pigmentary disturbance. Vision 6/9*

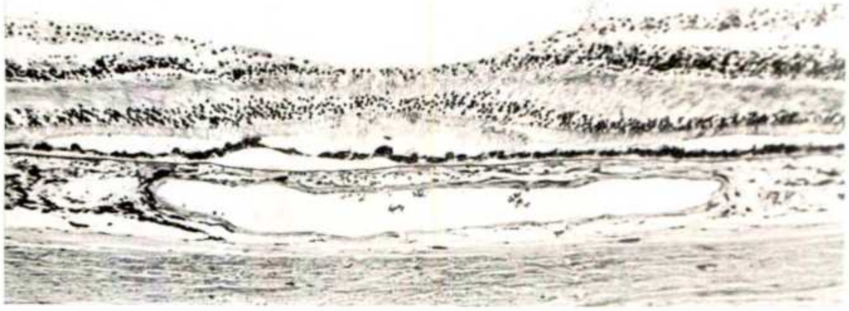


FIG. 12 *Section through macula of eye shown in Fig. 11. Note thinning of choroid accentuating prominence of larger vessels. Picro-Mallory.* × 90

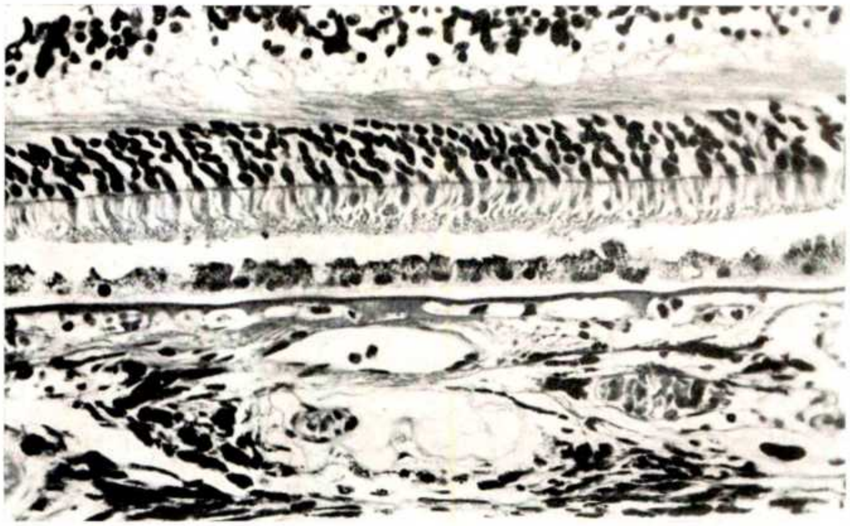


FIG. 13 *Section through paramacular area of same eye showing grade 3 hyalinization of Bruch's membrane and continuous basal linear deposit. Pigment cells show irregularity, cystic spaces, and indistinct cell outlines. In a choroidal artery there is replacement of muscle by fibrillar fibrous tissue. Picro-Mallory.* × 300

old man. Coarse clumps of pigment were distributed around a central hypopigmented area. Sections through this area showed the basal linear deposit to be much thickened and hyalinized, while the pigment epithelium remained only as a very attenuated layer and seemed about to disappear (Fig. 17). This was the most extreme example of thickening of the deposit found in Group IV, as in the other eyes it did not exceed the height of the normal pigment epithelium. Further, this group included three eyes in which the deposit did not show thickening although the pigment epithelium was similarly attenuated and formed occasional mounds of pigment granules. In these eyes the deposit was not hyalinized and appeared to have faded with the pigment epithelium.

Group V (Basal linear deposit with loss of overlying pigment)

In this group (24 eyes) loss of the retinal pigment epithelium produced areas of geographical atrophy visible clinically (Fig. 18). On histological examination the hyalinized basal linear deposit could be traced throughout the depigmented area in most eyes. The deposit also extended for some distance beneath the adjacent pigment epithelium, which showed the same changes as noted in Group IV. At the edge of the depigmented area the histological changes were constant. The pigment epithelium often ended in a group of proliferated cells, while the photoreceptors showed progressive degeneration as they approached the atrophic area in which they disappeared. The external limiting membrane ended in a curved line and the outer nuclear layer also disappeared so that the outer plexiform layer rested directly on the basal material (Fig. 19). Occasionally an island of persisting photoreceptors converged on a cluster of degenerating pigment cells. The choroid was often more atrophic in these eyes and many choroidal capillaries showed partial obliteration by fibrous tissue in the depigmented area. The narrowing of the capillaries often occurred abruptly where the pigment epithelium ended (Fig. 20). In relation to these capillaries Bruch's membrane appeared disproportionately

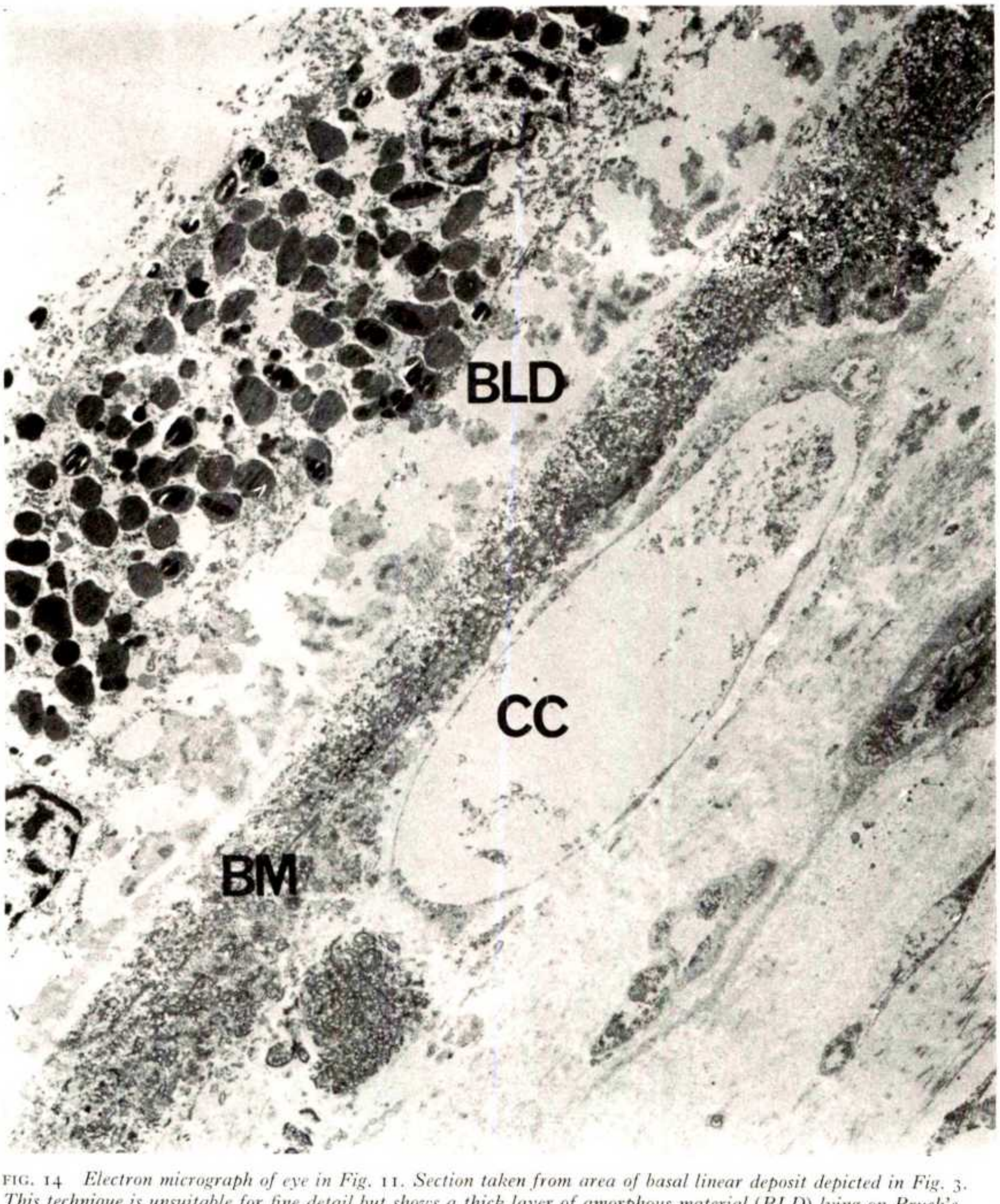


FIG. 14 *Electron micrograph of eye in Fig.* 11. *Section taken from area of basal linear deposit depicted in Fig.* 3. *This technique is unsuitable for fine detail but shows a thick layer of amorphous material* (*BLD*) *lying on Bruch's membrane* (*BM*). *The material in intercapillary pillars extends to level of outer surface of choriocapillaris* (*CC*) *and consists of irregular-banded collagen, vesicles, and tube-like structures.* × 6820

thick but in actual measurements the membrane was often thinner than in Group IV, particularly in those eyes in which clinical observation had confirmed the loss of the pigment epithelium to be of long standing (Fig. 21).

Fifteen eyes showed drusen of both types. All of the granular variety showed calcification and some also contained avascular fibrous tissue. Neovascularization from the choroid was demonstrated in 10 eyes, including six of the eyes with drusen,

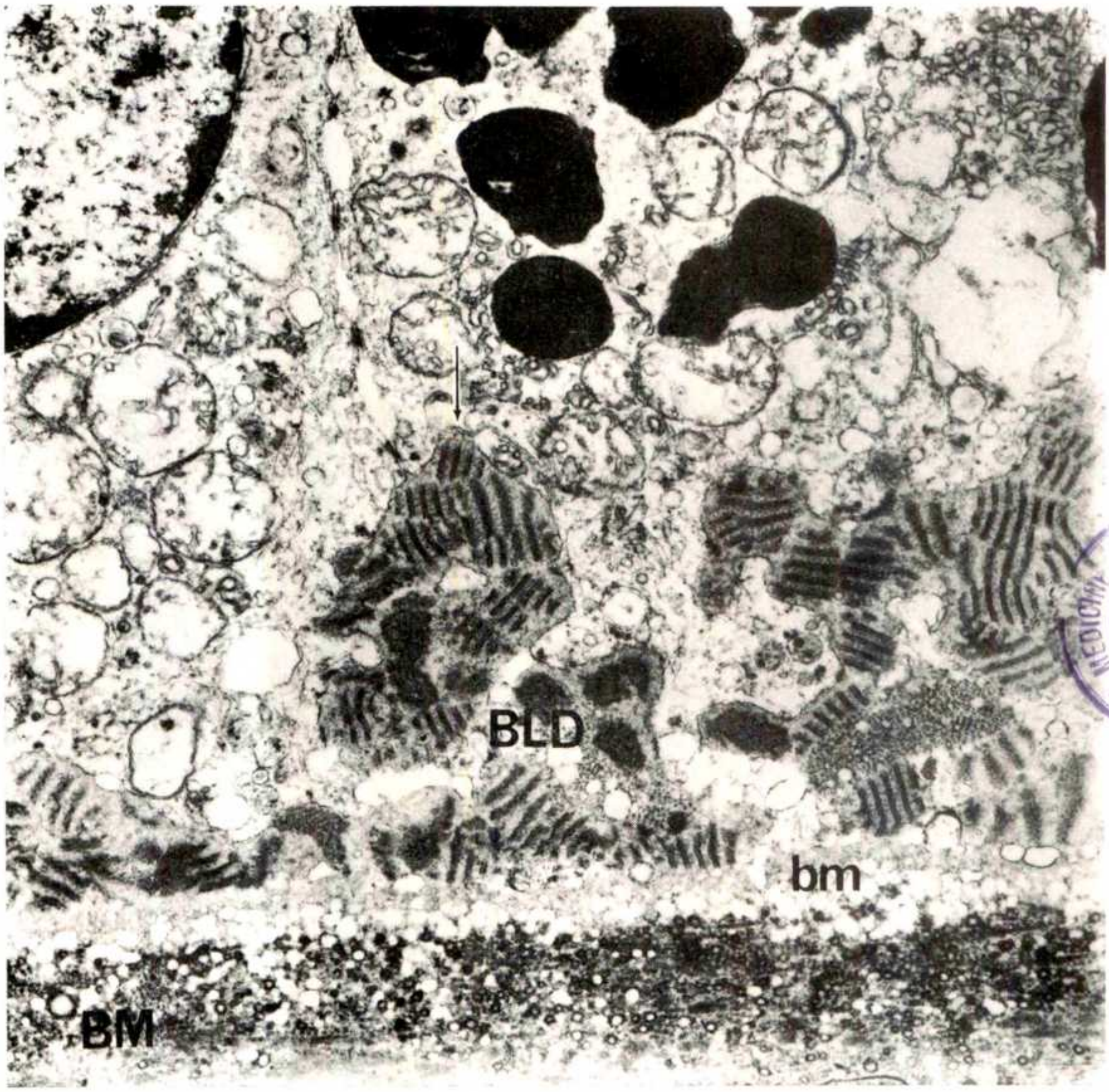


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FIG. 15 *Electron micrograph from macular region of man aged 71 whose fundus had shown coarse pigmentary changes. Histological examination of the fellow eye revealed thick basal linear deposit. The deposit (BLD) contains banded material lying between plasma infoldings of retinal pigment epithelium (arrow) and the basement membrane (bm). BM = Bruch's membrane.* × 19 250

and in seven eyes the breaks in Bruch's membrane were multiple. The fibrovascular tissue was more extensive than in Group IV but did not obscure the underlying choroid on clinical examination, unlike the thicker scars of disciform degeneration.

The areas of geographical atrophy were either present at the time of the first clinical examination or were observed to develop gradually within an area of coarse pigmentary mottling. The average age of patients in this group was 85·6 years and the most commonly recorded visual acuity when the fovea was involved was 3/60.

Group VI (Disciform degeneration)

In this group of 21 eyes fibrovascular invasion from the choroid resulted in clinically visible scars of varying size. The basal linear deposit remained identifiable as a hyalinized layer folded into the mass, sometimes separating fibrous tissue of different ages (Fig. 22). The deposit also extended for some distance beyond the scar and was attended by corresponding changes in the pigment epithelium and Bruch's membrane. Under the scar the choroid was generally thicker than in Group V and the arteries showed more pronounced sclerosis.

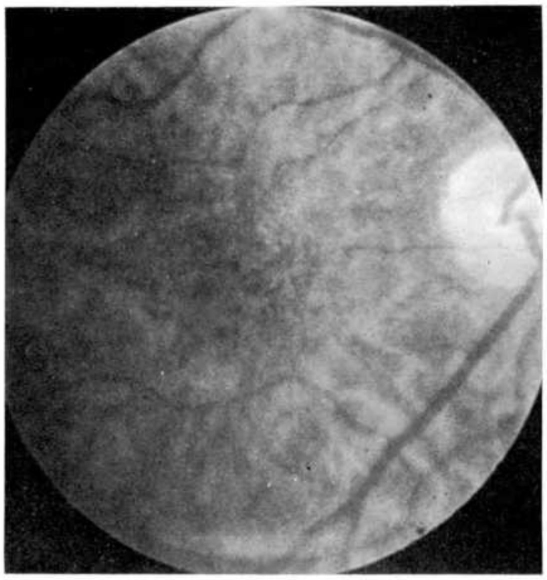

FIG. 16 *Tigroid fundus of 80-year-old man. Macula shows coarse clumps of pigment distributed around central hypopigmented area. Vision* 6/24

The average age of the 14 patients in this group was 81·9 years. Disciform degeneration was bilateral in seven patients while in four the second eye showed geographical atrophy which was also associated with new vessels. Although serous detachments of the retinal pigment epithelium were noted clinically during the evolution of disciform degeneration, only one eye subsequently showed such detachment on histological examination (Fig. 23). Fibrin was demonstrated in the serous fluid and vessels appeared to be extending into the serous detachment from an adjacent mound of fibrovascular tissue.

Cuticular material was occasionally observed in the scars, lying between rows or clusters of proliferating retinal pigment cells (Fig. 24). This material was eosinophilic, intensely positive to periodic acid-Schiff, and of hyaline appearance but stained blue with picro-Mallory, unlike the hyalinization of Bruch's membrane or of the basal linear deposit, which both showed a change in staining reactions to red with this method.

SENILE CHANGES IN CHOROID

The frequency with which the fundus presented a tigroid appearance rose sharply after the age of 75 years. This picture differed from the tigroid fundus seen in younger patients in that the choroidal vessels became visible beneath the macula and their margins were clear-cut. The senile halo was often pronounced (Fig. 11).

Although a pigmentary disturbance was commonly associated, the senile tigroid fundus was also observed in eyes in which the macula was otherwise normal. Histological examination confirmed that the clinical prominence of the vessels was due to thinning of the choroid, due particularly to loss of the middle layer, so that the larger vessels occupied almost the full thickness of the choroid (Fig. 12). Degenerative changes were also noted in some choroidal arteries similar to those seen in cerebral vessels, particularly in the choroid plexus. The vessels were shrunken and showed

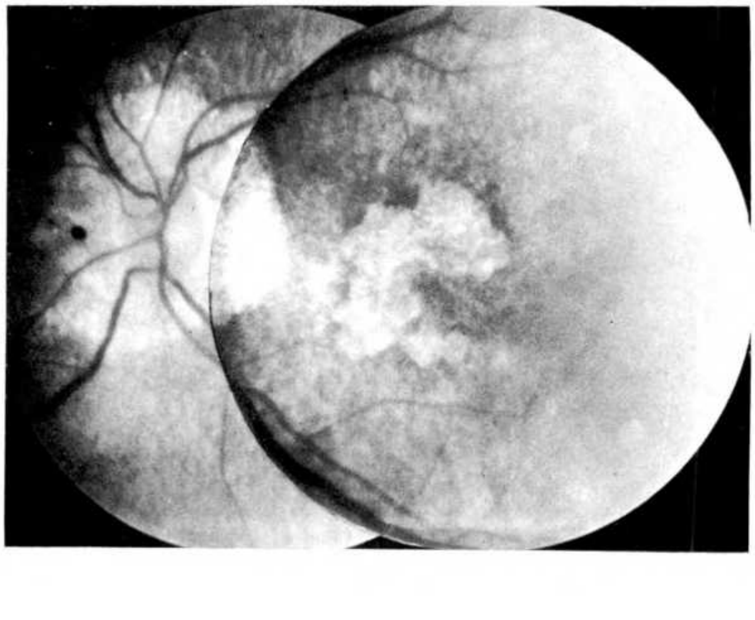

FIG. 18 *Left fundus of 84-year-old man first seen four years previously when fundus showed only peripapillary choroidal sclerosis and fine pigmentary disturbance at the macula. He gradually developed area of depigmentation nasal to the fovea, vision falling from* 6/9 *to* 6/24 *during this period*

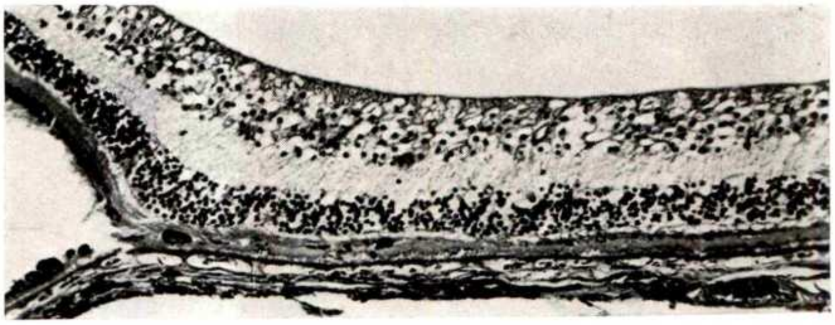

FIG. 19 *Section between macula (at left) and disc of eye in Fig. 18. There is loss of pigment epithelium, rod and cone processes, external limiting membrane, and outer nuclear layer. Outer plexiform layer rests directly on hyalinized basal linear deposit. Picro-Mallory.* ×150

replacement of muscle by fibrillar fibrous tissue (Fig. 13). The remains of occluded vessels with collapsed fibrous walls were also seen. The majority of the vessels, however, showed only fibrous replacement of the media with the retention of wide lumina. In normotensive patients hyalinization was observed only in extreme old age affecting the small vessels near the disc.

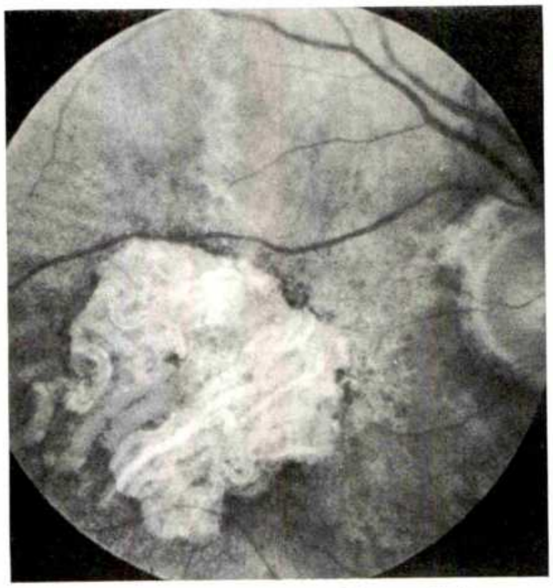

FIG. 20 *Right fundus of 83-year-old man suffering from central choroidal atrophy in both eyes. The areas increased slowly in size over period of six years. Note large vein which retains normal blood column. Vision was counting fingers in both eyes*

Discussion

In the elderly the macula typically shows loss of the foveal reflex, fine granularity of the retinal pigment, increased visibility of the choroidal vessels, and a few discrete drusen. These changes are considered to lie within normal limits, but in the present investigation 6/6 vision was recorded in fewer than half of the eyes showing these appearances and in none of such eyes belonging to patients aged 80 years and over. In most eyes this could be attributed to a failure of co-operation or to hazy media, but in others no cause was apparent. This decline in visual acuity with age was first noted by Donders (1864), and Weale (1975) calculated that the deterioration could be explained if the rate of cell fall-out found in the cerebellum was applied to the visual pathways. It follows that the limits of normal ageing are difficult to define in terms of fundal appearances or visual acuity.

The natural history of senile macular degeneration is similarly difficult to predict from clinical observation. Some cases show a progressive disturbance of retinal pigmentation, with or without prominent drusen, and culminate in geographical atrophy. During the evolution of the disease, however, the appearance of the choroidal vessels may become sufficiently abnormal to lead to the recognition of senile choroidal atrophy as a separate

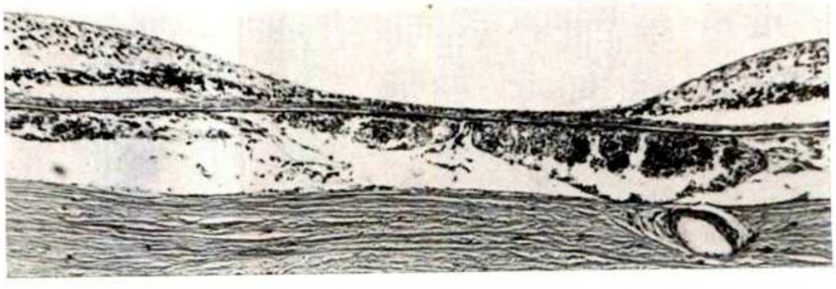

FIG. 21 *Section through macula of eye in Fig. 20. There is loss of retinal pigment epithelium and photoreceptors but basal linear deposit can be traced across depigmented area. The choriocapillaris is absent and dilated thin-walled vein occupies full thickness of choroid. Picro-Mallory.* ×75

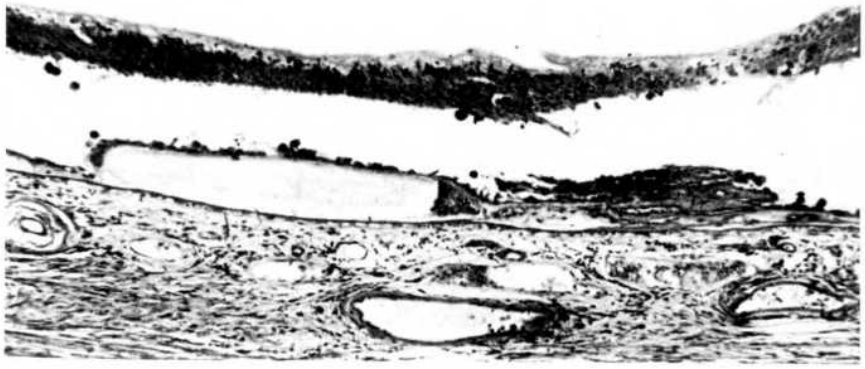

FIG. 23 *Right eye of 86-year-old man suffering from disciform degeneration. Section shows serous detachment of retinal pigment epithelium containing fibrovascular tissue, and an adjacent mound of cuticular material and proliferating pigment cells. Break in Bruch's membrane was remote from the detachment. Picro-Mallory.* ×75

entity. At other times subretinal exudation, haemorrhage, and neovascularization may occur to alter the clinical picture and influence the prognosis. In the present clinicopathological investigation, therefore, the changes associated with ageing and degeneration of the macula were recorded according to the degree of histological abnormality occurring at the level of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris.

BRUCH'S MEMBRANE

The age-related changes in Bruch's membrane comprised thickening and hyalinization, increased periodic acid-Schiff positivity, and basophilic staining. The use of the term hyalinization requires explanation, since it merely denotes that the membrane appears glassy or without structure. In the present discussion the term has been retained and has been applied when the membrane showed a change in staining properties from blue to red with the picro-Mallory method, increased periodic acid-Schiff positivity, and green staining with luxol fast blue. Picro-Mallory was one of several staining methods developed by Lendrum and others (1962) for the demonstration of fibrin, and Garner (1975) has suggested that the thickening of the membrane is due to the accumulation of plasma constituents secondary to undue permeability of the endothelium of the choriocapillaris. Staining with Mallory's PTAH, however, does not produce the dark blue appearance characteristic of fibrin, nor does the membrane subsequently develop the staining properties which Lendrum, Slidders, and Fraser (1972) found to accompany the ageing of fibrin. The change from blue to red staining of the membrane may be due to a reduction in the size of the intermicellar pores so that they accept only

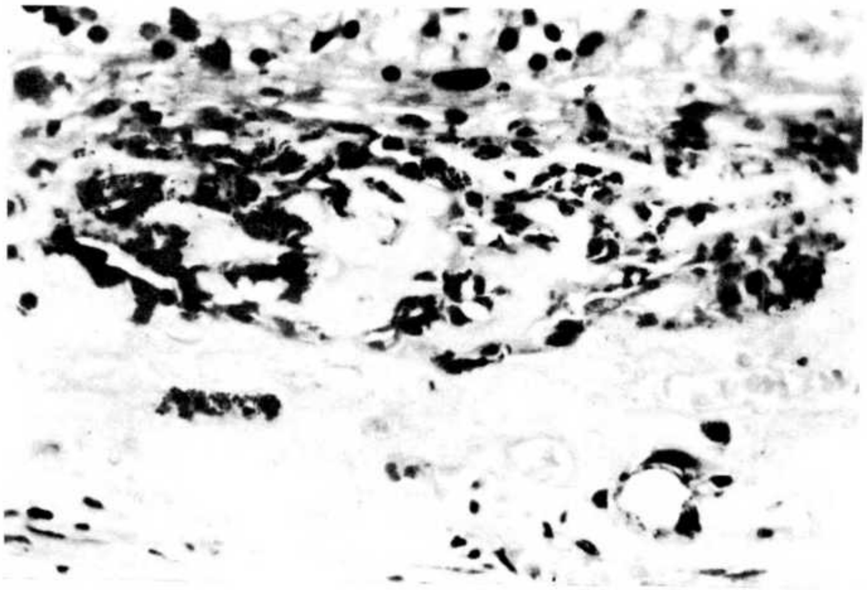

FIG. 24 *Section through eye of 75-year-old patient suffering from disciform degeneration. An irregular mass of hyaline cuticular material surrounded on all aspects by abnormal retinal pigment cells lies on inner aspect of fibrous tissue. Picro-Mallory.* ×500

the smaller molecule of the acid fuchsin dye. This explanation is suggested by the electron microscopic demonstration of increasing density of the membrane.

The electron microscopic changes which develop in the membrane with age appear to fall into two main groups. The accumulation of vesicular, granular, and filamentous material begins in the inner collagenous zone at around the age of 20 (Hogan, 1967). Residual bodies and undigested outer rod segments have been identified in this material which represents debris derived from the retinal pigment epithelium. On the other hand, after the age of 40 changes develop in the collagen and elastic fibres of the membrane. There is an increase of normal and intermediate collagen and of fibres resembling long-spacing collagen. Hogan, Alvarado, and Weddell (1971) also described long, coiled osmiophilic fibres which they suggested may be altered collagen fibrils on which an electron-dense substance is deposited. The elastic fibres also show increasing density and undergo calcification.

RETINAL PIGMENT EPITHELIUM AND BASAL LINEAR DEPOSIT

The earliest light microscopic evidence of degeneration of the retinal pigment epithelium was associated with the development of a finely granular deposit beneath the cells, although hyalinization of Bruch's membrane was already established. This material was simply described as a basal linear deposit in order to distinguish it from drusen. The deposit contrasted with the hyalinized membrane by staining blue with picro-Mallory, being only moderately periodic acid-Schiff positive and remaining unstained with luxol fast blue. Gass (1967) described this deposition as an eosinophilic granular material and noted that it stained blue with Masson's stain, suggesting a collagenous component to its composition. The electron microscopic findings (Figs 14, 15) show this deposit to lie between the basal plasma infoldings and the basement membrane of the retinal pigment epithelium and to consist mainly of spindle-shaped deposits, often embedded in a granular material. These deposits contained structures with widely-spaced striations with a periodicity of 120 nm, which Hogan (1972) considers to resemble short-segment, long-spacing collagen such as is obtained by the *in-vitro* precipitation of tropocollagen (Gross, 1957). Basement membrane is collagenous in nature and may briefly be defined as tropocollagen in carbohydrate-rich mucoprotein (Ashton, 1974). Tripathi (1974) suggested that under certain conditions long-spacing collagen may originate from a direct polymerization of basement membrane material.

Long-spacing collagen fibres have also been described in other tissues, notably in Descemet's membrane (Jakus, 1962), where they appeared to be the result of abortive attempts to form normal membrane (Hogan, Wood, and Fine, 1974), in the cortical zone of the trabecular beams (Garron, Feeney, Hogan, and McEwen, 1958), and in association with the basement membrane of the neuroepithelium of the utricular macula (Friedmann, Cawthorne, and Bird, 1965). Present indications are that these deposits which accumulate in the region of the basement membrane are a manifestation of gradual degeneration of the associated cells.

INTERPRETATION OF AGEING AND DEGENERATION IN MACULAR REGION ACCORDING TO BASAL LINEAR DEPOSIT

The development of the basal linear deposit beneath the retinal pigment epithelium appeared to be the most reliable histological criterion of the degree of degeneration of the overlying cells. The eyes were therefore classified according to the histological appearance of this deposit. Groups I and II broadly represented normal ageing, Groups III and IV represented the development and progress of degeneration, and Groups V and VI showed the subsequent end-results.

Groups I and II

In Group I the deposit could not be demonstrated although ageing of Bruch's membrane was already in evidence, starting in the fifth decade as patches of hyalinization under the macula and adjacent to the disc. With advancing age hyalinization and thickening spread over a wider area and also extended into the intercapillary pillars. The basal linear deposit first appeared in Group II in relation to thickened or basophilic segments of the membrane, or over the occasional widened intercapillary pillar showing hyalinization extending to the level of the outer surface of the choriocapillaris (grade 3). Nearly all eyes in these two groups retained a normal fundus appearance, often with 6/6 vision, and the histological changes were considered to be within the limits of normal ageing.

Groups III and IV

In Group III the basal deposit became a thin continuous layer and grade 3 hyalinization of Bruch's membrane extended for almost one disc diameter under the macula. These changes were considered to have become pathological, since more than half the eyes had developed a clinical disturbance of pigmentation and in most vision was reduced. In Group IV clinical abnormality was well established, manifest predominantly as coarse pigmentary clumping. This group was characterized by thickening of the basal deposit and more pronounced degenerative and proliferative changes in the pigment epithelium. Gradual disappearance of the cells led to the circumscribed areas of depigmentation which characterized Group V. A number of eyes appeared to show this transition, since they contained only a thin layer of pigment. In several eyes the deposit appeared to fade as the pigment epithelium disappeared, but in most it remained as a thickened hyalinized layer.

Neovascularization was first detected in Group IV, in which six of the 42 eyes (14·3 per cent) showed capillary membranes growing beneath the pigment epithelium in the macular region. These capillaries were found to be invading the basal linear deposit, and Gass (1967) also described capillaries coursing through this eosinophilic material in two cases. None of the eyes in Group IV showed evidence of a serous detachment of the pigment epithelium with which new vessels are commonly associated (Teeters and Bird, 1973*a*, *b*). The present series therefore appears to confirm the suggestion by the same authors that blood vessels may grow into the subpigment epithelial space without previous detachment of the pigment epithelium. The retinal pigment epithelium is normally firmly anchored to the choroid by fine filaments of the basement membrane which extend from its inner and outer surfaces to join the cell membrane and the inner collagenous zone of Bruch's membrane (Hogan and others, 1971), and probably the basal linear deposit disturbs this attachment. This may allow spontaneous detachment of the pigment epithelium to occur and may also predispose to the ingress and spread of new vessels. Further, the demonstration of macrophages and giant cells in relation to thinned but unbroken segments of Bruch's membrane suggests that there may be an attempt at organization, since in other tissues these cells may precede the appearance of granulation tissue.

Groups V and VI

In the later stages of macular degeneration the basal linear deposit becomes hyalinized and assumes the same staining properties as hyalinized Bruch's membrane. The deposit generally remains after the pigment epithelium has disappeared and traces of the deposit could be found in the depigmented area of all eyes belonging to Group V.

Commenting on the aetiology of these areas of geographical atrophy, Gass (1973) observed that most cases followed the fading of drusen but noted that this appearance could also result from the collapse of a serous detachment of the pigment epithelium. The latter mechanism was also proposed by Blair (1975), who thought that ischaemic changes in the underlying choriocapillaris would be less likely to produce such a well-demarcated area of atrophy. However, geographical atrophy was clinically observed to develop gradually within an area of coarse pigmentary mottling in several eyes in the present series. The histological studies also suggest that these depigmented areas evolve through the stages outlined, and in this respect to be determined by the initial changes in Bruch's membrane, retinal pigment epithelium, and choriocapillaris.

Neovascularization was demonstrated in 10 of the 24 eyes (41·7 per cent) in Group V. The fibrovascular invasion was more extensive than in Group IV but had not obscured the underlying choroid on clinical examination, unlike the thicker scars of disciform degeneration. The clinical picture is therefore determined by the extent of the neovascular response and different manifestations may occur in the two eyes. The more limited fibrovascular invasion associated with geographical atrophy may be related to the tendency for such eyes to show a greater degree of atrophy of all layers of the choroid, although it is more likely that the final result is dependent upon exudation and haemorrhage from the initial capillary membranes. Gass (1973) believed that geographical atrophy did not signify a basic difference from serous or haemorrhagic detachment of the retinal pigment epithelium and noted that disciform detachment sometimes occurred in the other eye. In the absence of neovascularization it is probable that geographical atrophy is the natural end-result and that this picture only becomes modified by an excessive degree of scarring.

In disciform degeneration the basal linear deposit becomes incorporated into the fibrovascular scar and the original derivation of the material is not readily apparent. Thus Green and Gass (1971) referred to the separation of the basal linear deposit from Bruch's membrane by fibrovascular tissue as a splitting of Bruch's membrane. The segments of hyalinized basal material which become enveloped by scar tissue and which no longer show any trace of the pigment epithelium are distinct from the laminated cuticular deposits found between rows of proliferating retinal-pigment cells. The latter material is also eosinophilic and strongly periodic acid-Schiff positive, but is of more hyaline appearance and stains blue with picro-Mallory. Cuticular material has been described in senile disciform degeneration (Verhoeff and Grossman, 1937; Frayer, 1955; Klien, 1951), fundus dystrophy

(Ashton and Sorsby, 1951), melanosis of the retina (Parsons, 1904), ringschweile of the ora in long-standing retinal detachment (Hogan and Zimmerman, 1962) and reactive proliferation of the retinal pigment epithelium (Tso and Albert, 1972), where the authors referred to it as basement membrane-like material. In several eyes in the present series the basal linear deposit resembled cuticular material, and the two deposits appear related.

DRUSEN

The incidence of eyes containing drusen in the macular region rose from 19·2 per cent in Group I to 52·5 per cent in Group V, due mainly to an increase in the granular variety. In the first three groups the drusen did not appear to affect vision, although none was located at the fovea. In Group IV, however, degeneration of the pigment epithelium was sometimes more pronounced over the larger deposits.

Drusen are a common clinical manifestation of the predisciform stage, but this investigation failed to find any histological evidence that drusen predispose to neovascularization. The drusen were not immediately related to the breaks in Bruch's membrane and any drusen in the vicinity of the new vessels appeared to be only the result of chance. Instead the vessels ramified within the basal linear deposit, and the drusen may simply be an independent manifestation of degeneration of the pigment epithelium. However, this series did not provide any information upon the relationship between drusen and pigment epithelial detachments.

In Group V drusen within the depigmented areas were observed clinically to become less prominent or to develop glistening foci of calcification. Gass (1973) noted that drusen in such an area may fade, and disappearance of some drusen was noted in the present series. Most, however, remained as calcified deposits, often partly replaced by avascular fibrous tissue.

CHOROID

Thinning of the choroid, interpreted as senile choroidal atrophy, became more common with advancing age. Clinically this was manifest as the senile tigroid fundus, the incidence of which rises sharply after the age of 75 (Sarks, 1974). This appearance has been termed depigmentation-*in situ* (Klien, 1958) and benign choroidal sclerosis (Archer, Krill, and Newell, 1971), the increased visibility of the choroidal vessels being attributed to disturbance of the overlying pigment epithelium. However, although degenerative changes in the pigment epithelium were commonly associated, the present investigation confirmed that the prominent choroidal pattern resulted when the larger vessels occupied a greater proportion of the attenuated choroid.

Senile choroidal atrophy was noted in all groups in this series and modified the clinical picture accordingly. This was particularly evident in Group V, in which the exposed vessels sometimes remained pink and at other times showed sheathing by white lines or appeared as solid white cords. The white lines of sheathing were caused by the disproportionate thickening of the lateral walls of the vessels which were flattened in the thinned choroid. The macroscopic dissection of several specimens showed that the vessels retained sufficient transparency for any contained blood column to become visible, suggesting that vessels which appeared as solid white cords no longer contained blood. Although degenerative changes were found in some choroidal arteries identical to those found in the ageing brain, most vessels showed only normal ageing changes with the retention of wide lumina.

Comment

Although senile macular degeneration seems inextricably bound to the ageing process the lack of universality suggests it is not essential to ageing. However, the mechanisms proposed to explain normal ageing can also be applied to the degenerative changes. Hogan (1972) believes there is a gradual run-down in the metabolic activity of the retinal pigment epithelium leading to the accumulation of metabolic waste in Bruch's membrane and consequent decrease in its permeability. The basal linear deposit subsequently develops over the more abnormal segments of the membrane and at this stage histological changes can be demonstrated in the retinal pigment cells. Clinical evidence of senile macular degeneration, however, does not develop until the changes become continuous under the macula.

Thickening of the basal linear deposit is associated with progressive degeneration of the pigment epithelium. If neovascularization does not develop, or if the fibrovascular response is limited, the natural end-result of this process is geographic atrophy. Since this is an uncommon manifestation and evolves slowly, useful vision may be retained for many years. Visual loss is accelerated when new vessels lead to complications, and treatment is therefore directed to their prevention or obliteration. However, since the histological abnormalities may extend over several disc diameters, the disciform response can be multifocal and particularly endangers the fovea where the changes are generally most severe.

Prophylactic photocoagulation may come into increasing use but as Bird (1974) points out, there are as yet no means of identifying those eyes at high risk from those at low risk. Drusen have been implicated in initiating the disciform response and in this study these were noted more frequently at the stage when neovascularization occurs, but the drusen were not related to the new vessels and may represent an independent expression of the metabolic failure of the pigment epithelium. The present investigation merely indicated that the eyes most prone to neovascularization were those with a coarse pigmentary disturbance and moderate visual loss whether drusen were present or not, and that the new vessels may also develop in the absence of pigment epithelial detachments.

Summary

Clinical and pathological examination was performed on 378 eyes from 216 patients aged 43 to 97 years. This series represented eyes in which the fundi were normal or showed various manifestations of senile macular degeneration. The eyes were divided into six groups according to the histological appearance of a linear deposit at the base of the retinal pigment cells. Groups I and II were considered to represent normal ageing, Groups III and IV the progressive development of senile macular degeneration, and Groups V and VI the end-results.

Group I showed no basal linear deposit. Thickening and hyalinization of Bruch's membrane was noted as early as the fifth decade. Group II showed patchy development of the basal linear deposit in relation to thickened or basophilic segments of Bruch's membrane, or over intercapillary hyalinization extending to the level of the outer surface of the choriocapillaris. Almost all eyes in these two groups retained a normal fundus appearance but visual acuity declined with age even in the absence of other causes. In Group III the basal deposit formed a thin continuous layer associated with moderate degeneration of the retinal pigment epithelium. More than half the eyes had developed a clinical disturbance of pigmentation and in most vision was reduced. Group IV was characterized by thickening of the deposit and more pronounced disturbance of the pigment epithelium. Clinically most eyes showed coarse pigmentary changes and vision was in the order of 6/24. 14·3 per cent of eyes in this group showed early neovascularization from the choroid. In Group V the pigment epithelium disappeared to produce circumscribed areas of depigmentation. The basal linear deposit could be traced throughout the depigmented area in most eyes. Thin fibrovascular sheets were found beneath the pigment epithelium in 41·7 per cent of eyes. Group VI represented disciform degeneration. The basal linear deposit could often be demonstrated as a disrupted hyalinized layer incorporated into the scar. Disciform degeneration was an alternative end-result to geographical atrophy. In each group the clinical and histological findings may be modified by the presence of drusen or by atrophy of the choroid.

The basal linear deposit consisted of banded fibres embedded in granular material lying between the plasma infoldings and the basement membrane of the retinal pigment epithelium. This deposit seems to be a manifestation of gradual failure of the pigment epithelium and proved to be the most suitable criterion by which to study the natural history of senile macular degeneration.

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Reticular dystrophy of retina

AMRESH CHOPDAR
From the Western Ophthalmic Hospital, Marylebone Road, London

This rare fundus dystrophy was first described by Sjögren (1950) in a Swedish family. Since then two more families have been described from Holland and Argentina by Deutman and Rumke (1969) and Alezzandrini (1971) respectively. This article describes a case in an Irish family.

Case report

The patient, a 7-year-old boy, was first seen at the Western Ophthalmic Hospital after a school medical examination showed he had poor visual acuity. He had no previous history of any systemic or ocular illnesses. His parents and grandparents were unrelated.

The best corrected visual acuity was 6/12 with +2·75 D cyl., axis 105° in the right eye and 6/9 with +2·50 D cyl. axis 80° in the left eye. External slit-lamp examination and ocular motility were normal. The fundi showed a small group of fine pigment clumps at each macula tightly enclosed within a small, light-coloured, ring-shaped area. The posterior part of the fundus showed extensive marking with thin pigmented lines forming a net-like pattern of polygons varying in size from half to one disc in diameter. The polygonal pattern was often incomplete. On slit-lamp examination with the contact lens it was clear that the pigment lay at the level of the retinal pigment epithelium. There was no pigment dispersion on the retinal surface except at the maculae. It was found that each pigmented line consisted of fine pigment granules of apparently uniform size. The junctional ends of these lines showed a slight increase in pigmentation. The retina beyond the dystrophy zone was normal. There was no evidence of optic atrophy or narrowing of the retinal blood vessels (Fig. 1*a*, *b*).

Fluorescein angiography showed marked choroidal background fluorescence in a typical fish-net pattern during the early part of the transit of the dye. The angiography also showed a wider area of involvement than was clinically apparent, extending slightly beyond the nasal border of the optic disc and the temporal vessel arcade. The dark central pigment clump at the macula was surrounded by a fluorescent ring corres-

Address for reprints: A. Chopdar, FRCS, Western Ophthalmic Hospital, Marylebone Road, London NW1

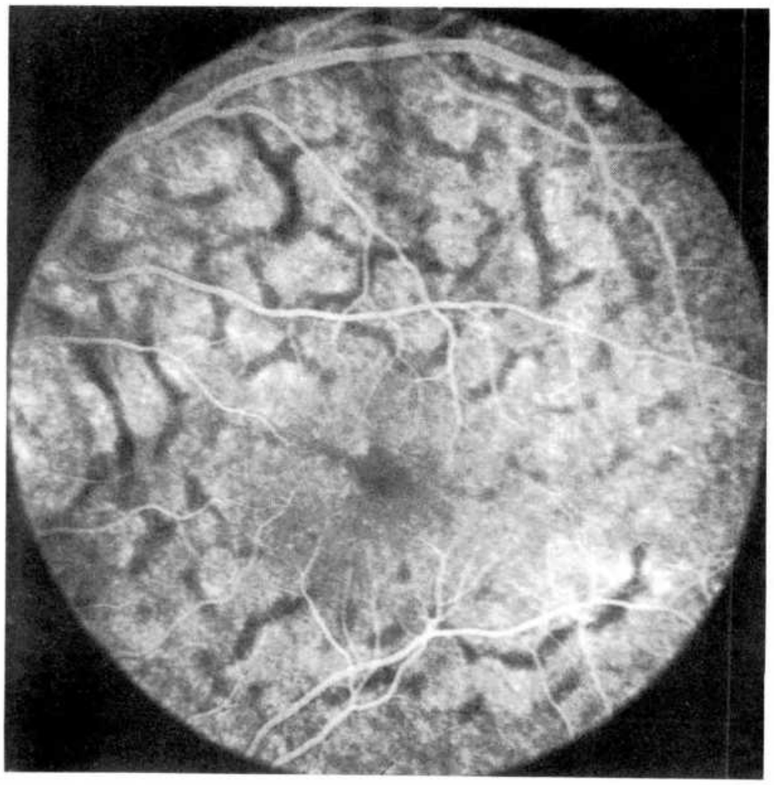

FIG. 2 (a) *Fluorescein angiography of left fundus during arterio-venous phase showing black markings on fundus in typical fish-net pattern masking choroidal background fluorescence*

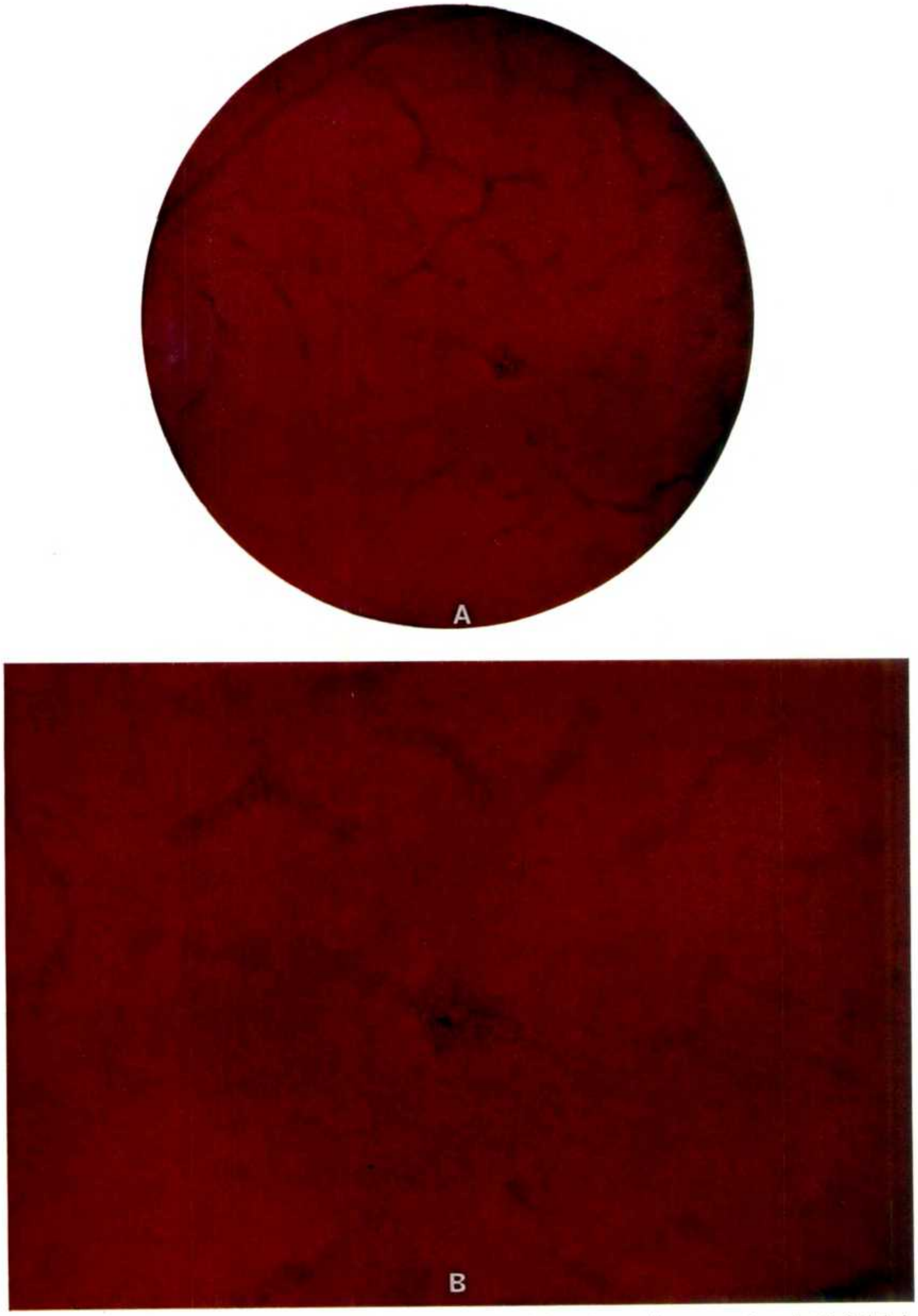

FIG. 1 (a) *Ophthalmoscopic view of left fundus showing typical reticular pigmentation at posterior pole.* (b) *Ophthalmoscopic view of central area of left fundus showing pigment clumping at the macula surrounded by pale ring*

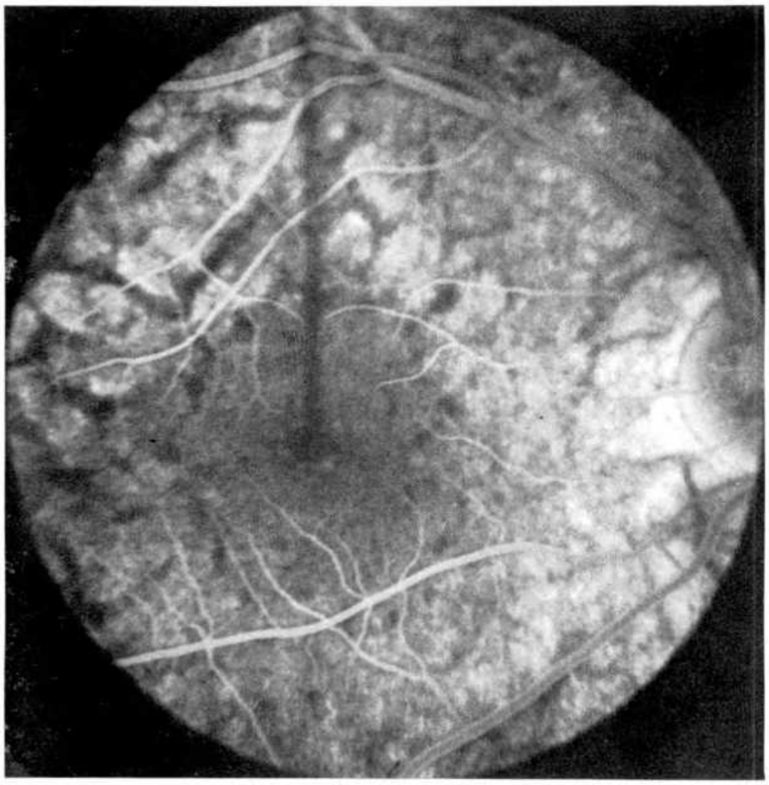

FIG. 2 (b) *Fluorescein angiography of right fundus during venous phase showing similar reticular pattern*

ponding to the pale area seen clinically. This was due to retinal pigment epithelial atrophy, allowing an easy transmission of the background fluorescence. There was no evidence of any leakage of dye at any stage of the angiography (Fig. 2*a*, *b*).

The patient's sister had no ocular abnormality. The father was myopic, one aunt suffered from myopia and squint, and three other aunts had refractive errors the nature of which was unknown. There was no evidence of consanguinity in the three generations of this family.

Two-and-a-half years later the patient's vision, refraction, and the fundus picture were unaltered.

RETINAL FUNCTION TESTS

Perimetry using a 3 mm white target did not show any field defect. Colour vision testing with pseudoisochromatic plates was normal in both eyes. The electroretinogram was normal in each eye with normal flicker (skin electrode), but the electro-oculogram was low at about 160 per cent in each eye.

Discussion

In this case of reticular dystrophy of the retina no other members of the family in three generations seemed to have been affected, although there were cases of squint and myopia. It is doubtful if these could be claimed as associated abnormalities. This is in contrast to the three other families reported, in which not only were other cases of reticular dystrophy found but there were also associated abnormalities such as spherophakia, intercalary staphyloma, shallow anterior chamber, and deaf-muteness (Sjögren, 1950). Deaf-mutism has been extensively studied by Holmsgren (1950) in the same family reported by Sjögren.

Summary

A case of an isolated occurrence of reticular dystrophy of the retina is described. The patient had no affected relatives.

I thank Mr R. J. Marsh for allowing me to study and publish this case, Mr Redmond J. H. Smith for his valuable criticism and help in preparing the manuscript, Mrs Ann Marie Turk for the illustrations, and Mrs Joyce Preen for secretarial help.

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Diagnostic features of the Favre-Goldmann syndrome

GERALD A. FISHMAN, LEE M. JAMPOL, AND MORTON F. GOLDBERG
From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago, Illinois

Traditional descriptions of the Favre-Goldmann syndrome include early onset of night blindness; atypical pigmentary dystrophy of the retina; degenerative changes of the vitreous humour (including both liquefaction and the presence of microfibrillar strands); peripheral and, less often, central retinoschisis; lens opacities; striking electroretinographic (ERG) abnormalities; and autosomal recessive inheritance. We noted previously unreported diffuse leakage from retinal vessels on fluorescein angiography. Electroretinography showed cone and rod responses which we believe are characteristic in the earlier stages of the disease.

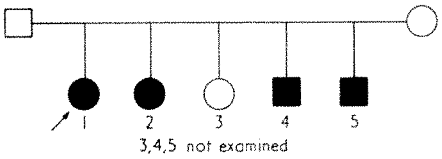

FIG. 1 *Pedigree of cases 1 and 2. Arrow identifies proband.*

Case reports

CASE 1

A 27-year-old White woman (the proband) was first seen at the University of Illinois Eye and Ear Infirmary in December 1974 for investigation of poor vision in her right eye and decreased night vision for as long as she could remember. Neither symptom had worsened. The patient had no other subjective complaints. She had completely recovered from hepatitis two years previously. The patient was not taking any medications, although she had taken oral contraceptives in the past. Two younger brothers, aged 18 and 22 years, were reported also to have poor night vision. A 16-year-old sister had no ocular complaints. Parental consanguinity was not noted. The case of another younger sister who also complained of poor night vision is described later. Fig. 1 illustrates this pedigree. The patient's two-year-old daughter and five-month-old son were ophthalmoscopically normal.

The patient's best corrected visual acuity was 20/200 in the right eye with −4·00 sph. +1·25 cyl. ×115°, and 20/20 in the left eye with −1·25 sph. +1·00 cyl. ×30°. External examination showed a mild blepharoptosis on the left; the conjunctiva and cornea of both eyes were normal. The patient's right pupil was slightly smaller than the left; no Marcus Gunn phenomenon was demonstrated, and both pupils reacted normally to both direct and consensual light stimuli. The left iris had a more greenish hue than the blue right iris. Motility examination showed a right hyperphoria and slight overaction of the right inferior oblique muscle. On slit-lamp examination the cornea and anterior chamber were normal. The right lens showed a 1+ posterior subcapsular lens opacity while the left lens was clear. The vitreous humour of both eyes was optically empty posteriorly, while anteriorly microfibrillar strands of condensed vitreous were noted. Intraocular pressures were normal in both eyes. Visual field testing showed a symmetrical constriction to within 20° of fixation with a 4 mm white test object in the right eye and to within 15° to 20° of fixation with a 2 mm white test object in the left eye.

The right fundus showed extensive peripheral retinoschisis beginning between the equator and ora serrata and extending posteriorly to the superior and inferior temporal vessel arcades. Nasally, the schisis did not extend more than 1 disc diameter posterior to the equator. Clumping of retinal pigment was seen predominantly in areas of retinoschisis. The schisis and pigmentation were greater temporally than nasally. The optic disc appeared normal. The macula had minimal but definite cystoid changes. In the posterior pole, but not in the macula, subtle, white, thread-like opaque changes were noted within the retinal vessels. As peripheral, more highly raised areas of schisis were approached these opaque changes became more evident in small retinal vessels and often assumed a dendritic appearance (Fig. 2). Similar but less extensive changes were noted in the patient's left eye. In addition to the areas of extensive schisis and opaque vascular changes a full-thickness retinal hole with an operculum was noted at 11 o'clock near the equator in the left eye. A small vitreous traction band extended from the operculum over the ora serrata.

A dark-adaptation study with a Goldmann-Weekers dark adaptometer showed monophasic curves in both eyes. Final cone thresholds were normal, while a rod component to the dark-adaptation curve was nondetectable. An electro-oculogram (EOG) showed

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Address for reprints: G. A. Fishman, MD, University of Illinois Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, Illinois 60612, USA subnormal light-peak to dark-trough ratios of 1·71 and 1·62 in the right and left eyes, respectively. An ERG showed cone responses that were normal in amplitude but much prolonged in implicit time in both eyes (Fig. 3*a*). During a 15-minute period of dark adaptation the responses did not change in either implicit time or amplitude. A small b_2 (probable rod component of the scotopic ERG) was noted (Fig. 3*b*). A I-4 blue stimulus from a Grass photostimulator was implemented to isolate rod responses and showed a minimal 25 μV b-wave deflexion from the baseline while an I-16 red stimulus showed only cone (x-wave) responses in both eyes. Flicker fusion frequency testing of both eyes with a high-intensity stimulus showed fusion at 30 cycles/s. Normal fusion frequency rates are 55 cycles/s or higher.

A fluorescein angiogram accentuated the opaque retinal vessels in the temporal periphery of the patient's right eye. Within areas of most advanced schisis opaque retinal vessels were not perfused (Fig. 4*a*). In less raised areas delayed perfusion of some remaining opaque vessels was seen (Fig. 4*a*). Vessel perfusion often appeared to end just posterior to extensive raised areas of schisis (Fig. 4*a*). Fluorescein leakage occurred from opaque retinal vessels at the margin of perfused and non-perfused retina (Fig. 4*b*). These leaking vessels did not represent neovascular tissue. A late-phase fluorescein study of the patient's right macula showed subtle but definite leakage from perifoveal capillaries (Fig. 5) and throughout the posterior pole.

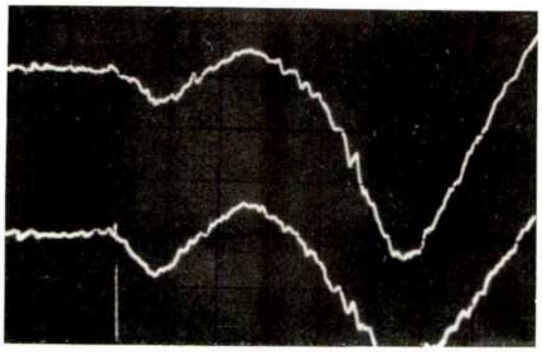

FIG. 3a *Case* 1. *Light-adapted ERG. Both right (upper) and left eye (lower) tracings show prolonged implicit times of 50 ms. Vertical squares represent 100 μV, horizontal squares 20 ms. Normal cone implicit time, from vertical line, lower left, to b-wave peak is 28 ms*

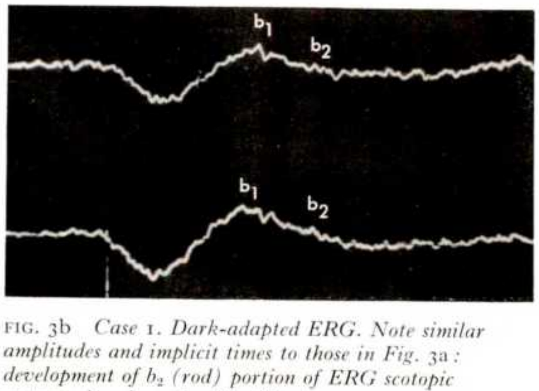

FIG. 3b *Case* 1. *Dark-adapted ERG. Note similar amplitudes and implicit times to those in Fig.* 3a*: development of b_2 (rod) portion of ERG scotopic response is only noticeable difference*

CASE 2

The 26-year-old sister of case 1 was seen in January 1975 for investigation of poor night vision since early childhood. The patient's general health was good. Her best corrected visual acuity was 20/25 in the right eye with +5·75 sph. and 20/30 in the left eye with +3·25 sph. +0·25 cyl. × 10°. External examination was normal. Versions were full in all directions of gaze. The pupils reacted normally to both direct and consensual light stimuli. Although orthotropic for near, the patient did have a variable 25 to 30 prism dioptre alternating esotropia for distance. Slit-lamp examination of the cornea and anterior chamber was normal in both eyes. There was no evidence of any iris heterochromia. The patient had 1+ bilateral posterior subcapsular lens opacities and 1+ cells in the mid-vitreous cavity. The vitreous humour in both eyes appeared optically empty posteriorly while the anterior vitreous showed degenerative microfibrillar strands. On gonioscopy the anterior chamber angles were normal. Fundus examination revealed subtle cystoid changes. The larger retinal vessels appeared to be normal in both calibre and course. An extensive shallow retinoschisis was noted throughout the mid-periphery of both eyes. The schitic changes, which were associated with a moderate amount of black pigment clumping, were present both nasally and temporally. Opaque vessel changes were present throughout the mid-periphery extending anteriorly between the equator and ora serrata (Fig. 6).

Visual field testing with a Goldmann perimeter showed relative symmetrical constriction to within 15° of fixation in each eye. Results of a dark-adaptation test were similar to those in case 1 in showing only a monophasic recording with normal final cone thresholds. Colour vision testing with the Farnsworth-Munsell 100-hue test showed a mild blue defect in the patient's right eye and normal colour perception in the left. An EOG showed significantly abnormal light-peak to dark-trough ratios of 1·33 and 1·05 in the right and left eyes, respectively. (Normal values for her age from our laboratory would be 1·75 or greater.) An ERG showed cone responses that were both reduced in amplitude and prolonged in implicit time. After a 20-minute period of dark adaptation there was essentially no change from photopic values in either amplitudes or implicit times in either eye, reflecting an apparent absence of detectable rod activity. Rod responses were also non-detectable with a low-intensity I-4 blue stimulus. Flicker responses with a high-intensity stimulus were non-detectable at 30 cycles/s.

A fluorescein angiogram of the patient's right eye showed extensive leakage from retinal capillaries throughout the posterior pole (Fig. 7). Leakage was present in the mid-periphery in association with vessels

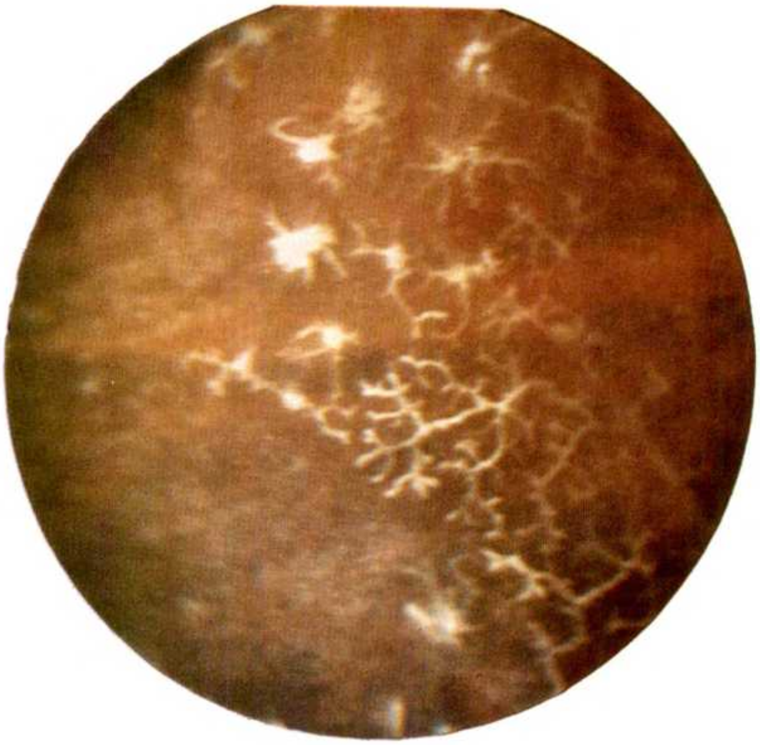

FIG. 2 *Case 1, right eye. Opaque, dendritic appearance of peripheral vessels*

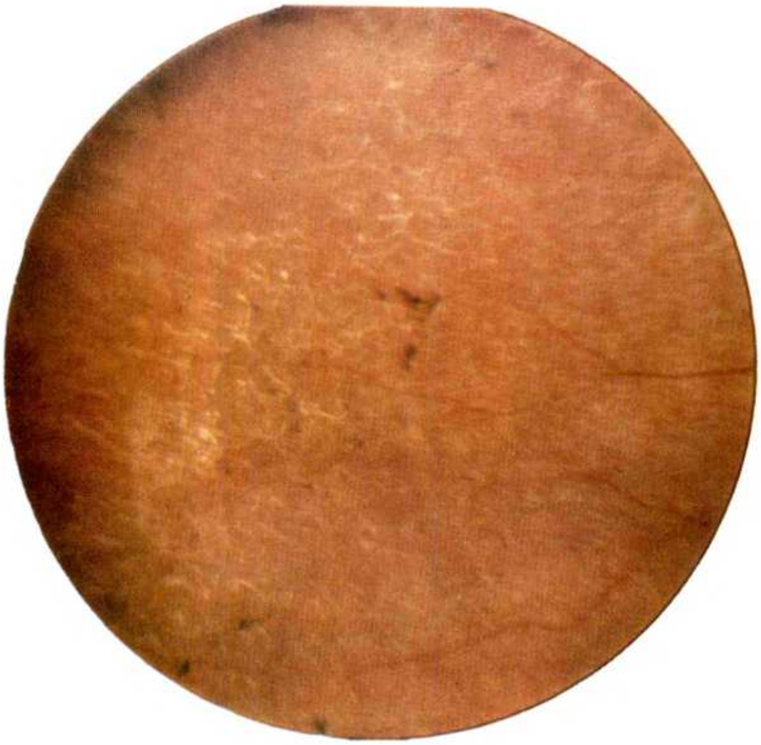

FIG. 6 *Case 2. Opaque vessels within mid-periphery of right eye*

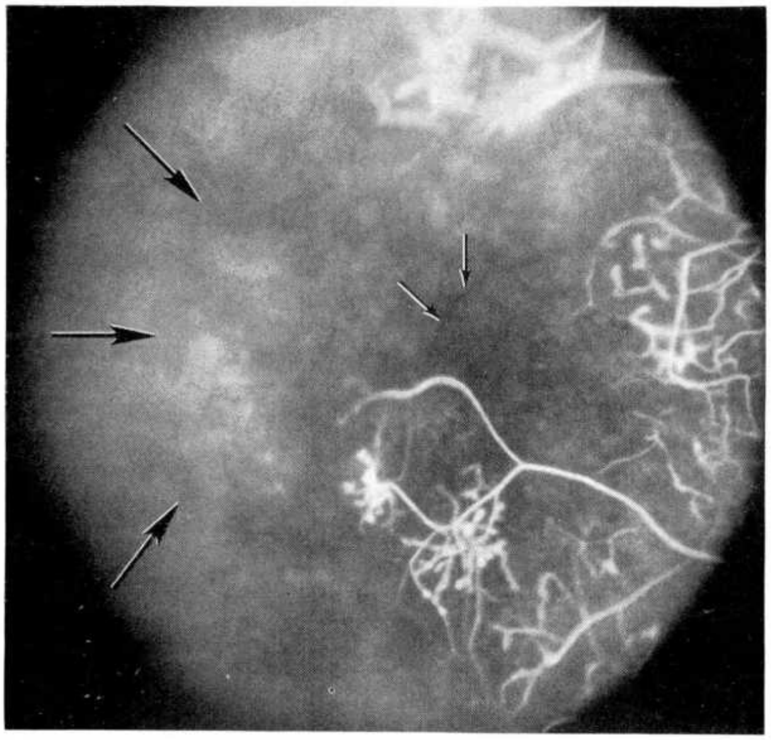

FIG. 4a *Case 1. Fluorescein angiogram of temporal periphery from right eye showing opaque, dendritic retinal vessels. Non-perfused retina is noted within areas of marked schisis (larger arrows). Note delayed filling of retinal vessel (smaller arrows)*

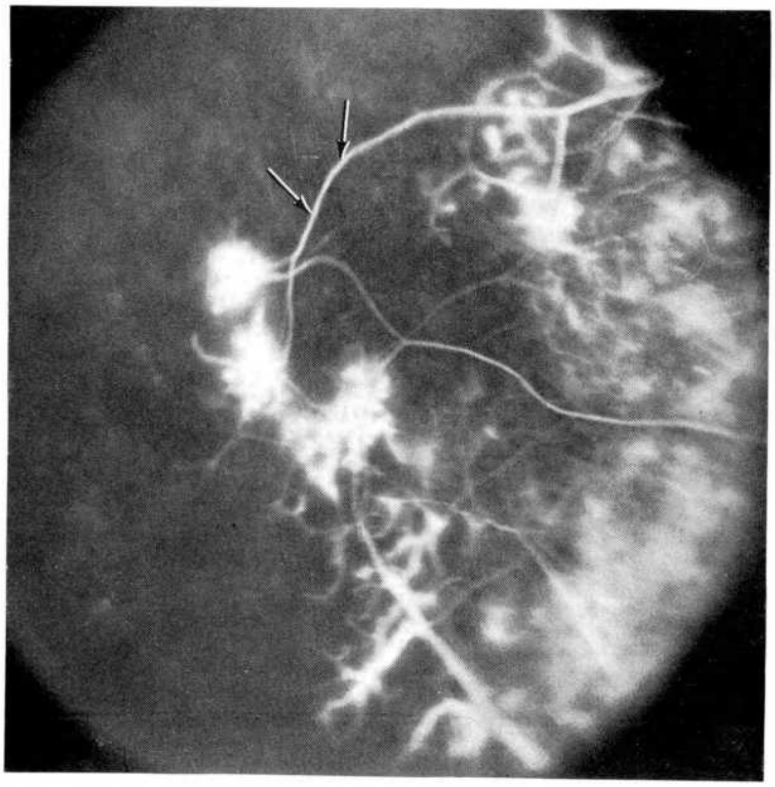

FIG. 4b *Leakage of dye from opaque retinal vessels at margin of perfused and non-perfused retina. Note same vessel in Fig. 4a is now perfused (arrows)*

that ophthalmoscopically were opaque. Less leakage occurred in areas where retinoschisis was most evident clinically. Areas of early hyperfluorescence noted in the posterior pole and mid-periphery were associated with retinal pigment epithelial atrophy while spotty regions of hypofluorescence were caused by pigment clumping. In later stages of the angiographic study changes of cystoid oedema were noted in the right macula (Fig. 7).

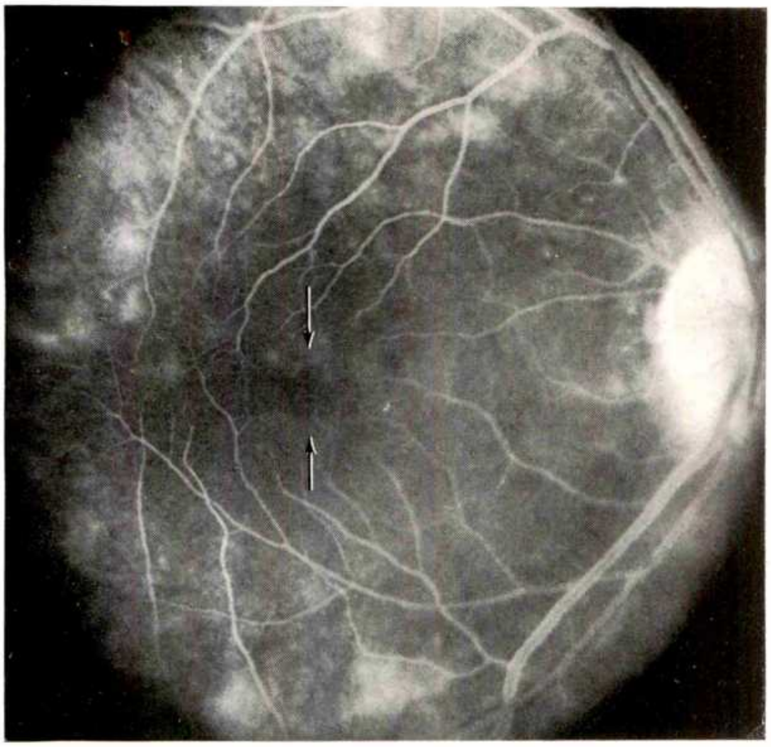

FIG. 5 *Case 1. Late-phase fluorescein angiogram from the posterior pole. Note leakage from perifoveal (arrows) and other capillaries*

CASE 3

A 56-year-old White man, who was unrelated to the patients in cases 1 and 2, complained of decreased night vision and poor peripheral vision for as long as he could remember. The central vision in his left eye had also been poor since about age 20. Vision in the right eye had been good until about 10 years previously, when he began to notice a slow but progressive decrease in acuity. The patient's general health was good. A 55-year-old sister, unavailable for examination, also complained of poor night vision since childhood. Parental consanguinity was not noted.

Visual acuity was 20/60 in the right eye with +6·75 sph. +1·75 cyl. × 180° and 5/200 in the left eye with +6·00 sph. External and motility examinations were normal. Slit-lamp examination of the cornea, iris, and anterior chamber of both eyes was normal. Both pupils reacted normally to direct and consensual light stimuli. Ocular pressure was 11 mmHg in each eye. There were bilateral 2+ posterior subcapsular lens opacities. The vitreous humour in both eyes was optically empty posteriorly from extensive liquefaction, while in the anterior vitreous chamber there were spidernet fibrillar strands. Fundus examination showed a bilateral waxy-type atrophy of the optic discs and constricted retinal vessels. The foveal reflex was absent in both eyes. Within the superior and inferior temporal mid-periphery of the right eye was a highly raised retinoschisis (Fig. 8). In some areas the schisis extended posteriorly, and ophthalmoscopically appeared to end just posterior to the arcade formed by the large superior and inferior temporal arterioles (Fig. 9). The schisis was progressively less raised posteriorly as it approached the borders of the superior and inferior temporal vessels. All schitic areas were associated with round black clumps of retinal pigment (Figs 8, 9). On slit-lamp examination of the posterior pole with a contact lens subtle opaque changes were noted within smaller retinal vessels not associated with areas of schisis. These opaque changes became more evident as the vessels approached regions of shallow schisis. At the posterior border of more raised schitic areas the opaque vessels were most evident and appeared dendritic. Although areas of schisis were not noted nasal to the optic disc minimal opaque changes within smaller retinal vessels were also present in these areas. Fundus changes in the left eye were essentially the same as those in the right.

Visual field testing with 4e-III and 4e-IV isopters on the Goldmann perimeter showed an absolute symme-

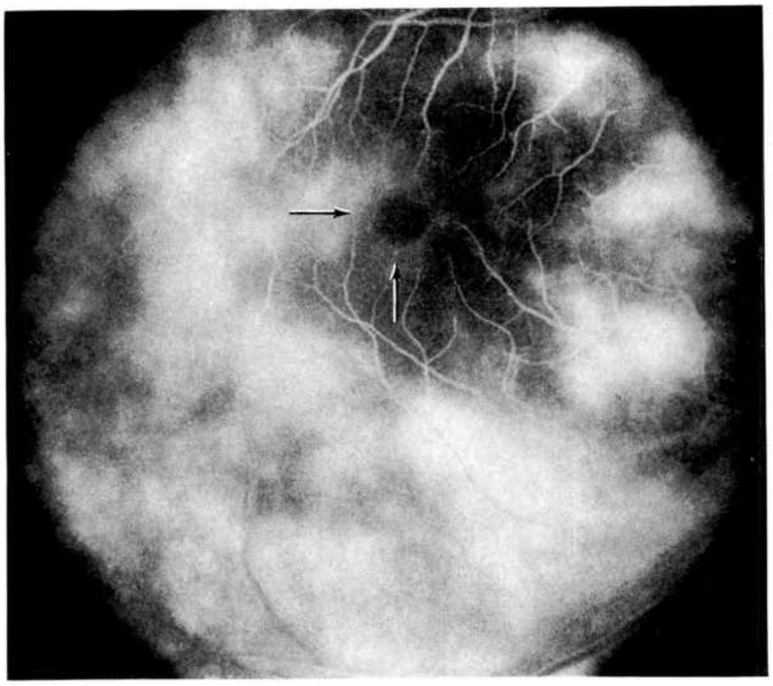

FIG. 7 *Case 2. Extensive leakage from retinal capillaries throughout posterior pole. Note leakage from perifoveal capillaries (arrows)*

trical constriction to within 15° of fixation in each eye. Dark-adaption thresholds measured on the right eye showed a monophasic curve with a normal cone threshold. In both eyes ERG responses were non-detectable, while an EOG showed light-peak to dark-trough ratios of 1·10 and 1·15 in the right and left eyes, respectively. On fluorescein angiography leakage from retinal capillaries was evident even in areas which ophthalmoscopically either appeared normal or showed only subtle opaque changes within retinal vessels. Extensive capillary leakage was noted posteriorly in areas of low schisis (Fig. 10). Retinal capillaries were non-perfused in areas where schisis was much raised in the mid-periphery.

Discussion

Favre (1958) reported vitreoretinal degeneration and the early onset of poor night vision in a 16-year-old boy and his 15-year-old sister. Vitreous changes included both liquefaction and fibrillar degeneration. Fundus changes included equatorial chorioretinal atrophy and pigment clumping. Peripheral and macular retinoschisis was also noted. Ophthalmoscopically the schisis of the macula was reminiscent of microcystic oedema. The boy also had posterior cortical lens opacities. In both cases visual field testing showed annular scotomas, while dark-adaptation studies revealed monophasic curves with normal cone but absent rod thresholds. Their 13-year-old sister was normal, and a paternal grandmother, although not examined by Favre, was reported by the family to have had poor night vision. Ricci (1960) found that ERG responses were non-detectable in Favre's two patients. He reported similar findings in a 41-year-old woman and emphasized the absence of an ERG response. Ricci suggested an autosomal recessive pattern of inheritance.

In the majority of similar cases subsequently reported (Blanck, Polliot, and Bernard, 1973; Carr and Siegel, 1970; François, De Rouck, and Cambie, 1974; François and Van Oye, 1967; MacVicar and Wilbrandt, 1970; Maraini, 1967; Stankovic, Kecmanovic, and Drincic, 1973) ERG responses were non-detectable. Dark-adaptation findings generally included monophasic curves with normal cone thresholds or biphasic curves with much raised rod final thresholds. Recordable ERG responses were noted by Carr and Siegel (1970) in an 11-year-old boy with Favre-Goldmann syndrome. The photopic a- and b-waves were described as 'near normal'; a scotopic increment was not observable. No mention was made of implicit time values. The same authors reported an additional case of a 22-year-old man who had a normal ERG photopic and scotopic a-wave but an absence of any positive b-wave response. Since selective absence of an ERG b-wave is characteristic of juvenile X-linked retinoschisis it was not clear from their description how they eliminated this diagnostic possibility.

Recordable but markedly reduced a- and b-wave ERG responses were obtained from a single case

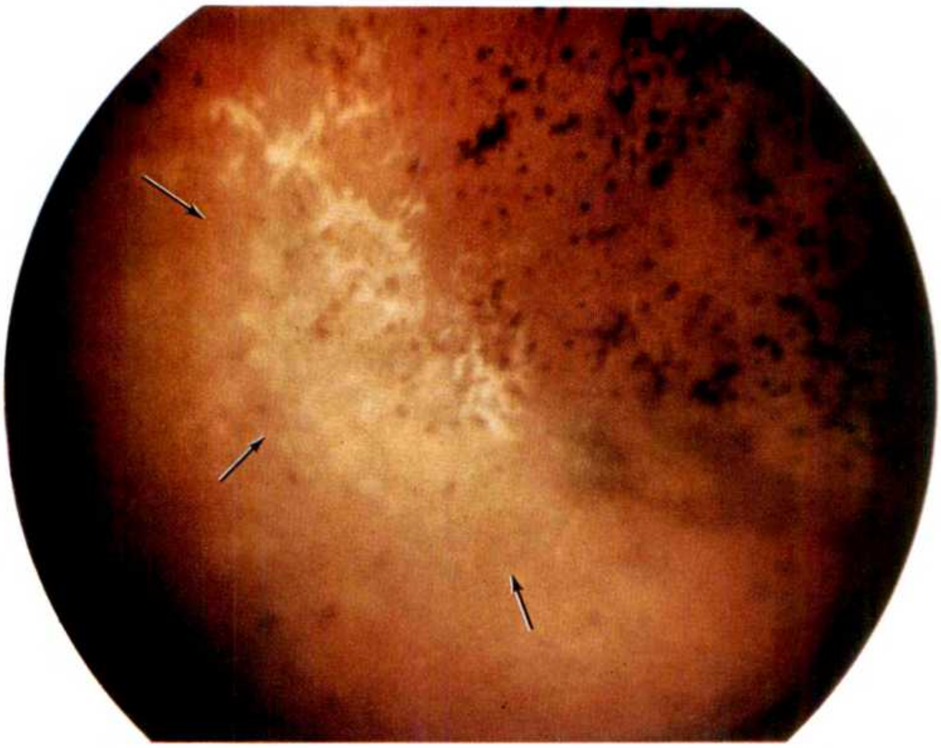

FIG. 8 *Case 3. Highly raised retinoschisis in temporal periphery from right eye (arrows). Clumping of retinal pigment epithelium is seen*

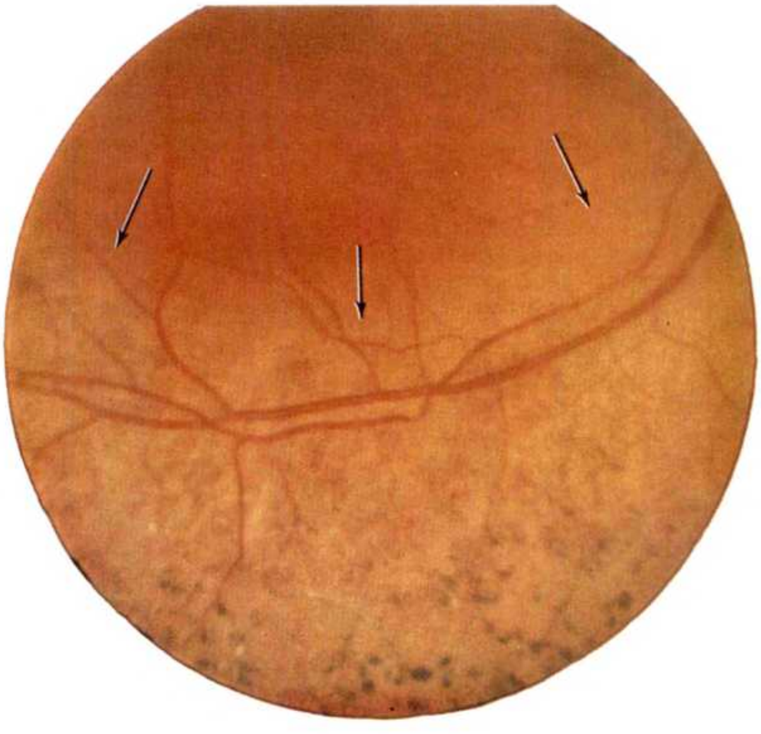

FIG. 9 *Case 3. Posterior extension of schisis to within inferior vascular arcade (arrows)*

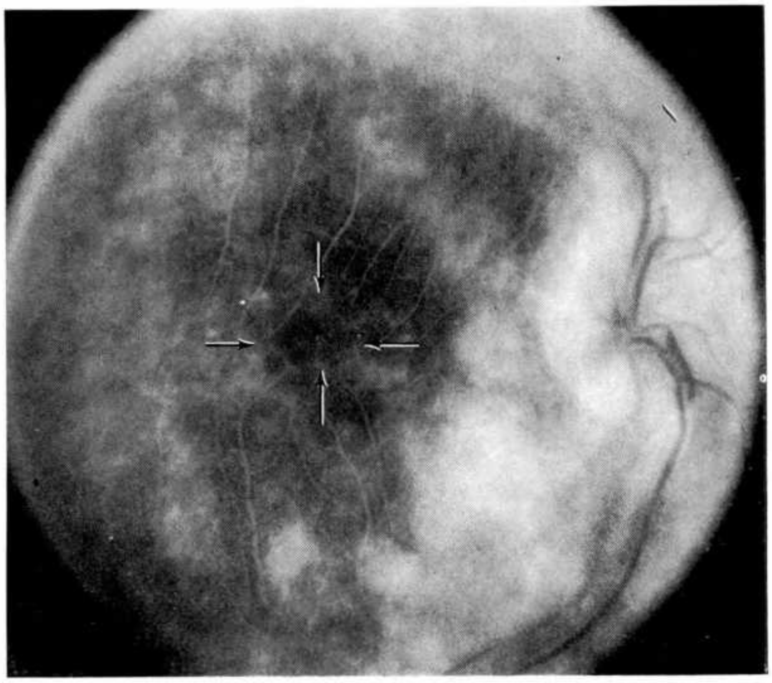

FIG. 10 *Case 3. Extensive leakage from retinal capillaries in posterior pole. Note leakage from perifoveal capillaries (arrows)*

reported by Blanck and others (1973). Implicit time values were not cited. In three cases reported by François and others (1974) photopic responses of either normal or subnormal amplitudes were noted. Photopic implicit times were prolonged in two of the three cases. Scotopic recordings showed either absent or much decreased b-wave amplitudes. Scotopic a-waves were recordable but reduced in amplitude. In our two younger patients, on whom ERG responses were still recordable, photopic and scotopic amplitudes were essentially identical. The photopic responses were either normal or subnormal in amplitude and prolonged in implicit time. Prolonged cone (photopic) implicit times have also been noted in most genetic patterns of retinitis pigmentosa (Berson and Kanters, 1970). In our patients ERG rod responses either failed to develop or developed minimally after 15 minutes of dark adaptation. The scotopic responses in Fig. 3*b* are presumably predominantly from cone activity, thus accounting for the almost identical responses under both light- and dark-adapted conditions. Highly abnormal flicker fusion frequency responses in the presence of normal or slightly subnormal ERG single-flash photopic amplitudes were an unexpected finding in two of the three cases. This discrepancy between single-flash photopic amplitudes and flicker fusion frequency has not been previously emphasized and may be characteristic of this disease.

Two reports of fluorescein angiographic findings in patients with Favre-Goldmann syndrome made no mention of either leakage from or non-perfusion of retinal vessels (MacVicar and Wilbrandt, 1970; Stankovic and others, 1973). The diffuse vascular leakage noted in our patients is unique among retinal dystrophies and has not been reported in association with peripheral or macular changes in X-linked juvenile retinoschisis. Isolated reports have described perifoveal capillary leakage and cystoid macular oedema in patients with retinitis pigmentosa (ffytche, 1972; Gass, 1970). Since cystoid macular oedema was present in varying degrees in all three of our patients we suspect that at least some previously reported cases of Favre-Goldmann syndrome with 'macular schisis' may have had microcystic oedema from leaking perifoveal capillaries.

Dendritic opaque vessels similar to those seen in our cases have been noted in patients with juvenile X-linked retinoschisis. We observed a correlation between the presence of schitic changes and the development of vessel opacity, leakage, and non-perfusion. No retinoschisis was present in the posterior pole and only subtle opaque vascular changes were noted on contact lens examination. Even these mildly opaque retinal vessels were, however, incompetent, as evidenced by leakage of fluorescein. Moderate retinoschisis was present within the mid-peripheral retina in association with marked opaque vascular changes and extensive leakage of fluorescein dye. In areas with the most extensive schitic changes retinal vessels no longer appeared opaque but were non-perfused. A cause and effect relationship between non-perfusion and opaque retinal vessels and the development of retinoschisis cannot be supported with certainty by our findings. However, possibly those areas with extensive ischaemia of the inner retina are most susceptible to the development of schisis. An equally tenable explanation might implicate the schisis as causing secondary non-perfusion of retinal vessels. Other forms of retinoschisis do not cause a similar diffuse vascular leakage, and therefore another sequence of events (vascular leakage causing perivascular fluid accumulation and thereby retinoschisis) may apply to the Favre-Goldmann syndrome and may be analogous to the pathogenesis of cystoid macular oedema in this syndrome. In this disorder, as exemplified by case 2, ultimate occlusion of previously leaking vessels may result in a clinical situation characterized by maximum raising of schitic areas with absence of leakage (owing to total non-perfusion of previously involved vessels).

A diagnosis of Favre-Goldmann syndrome should be considered in patients presenting with an early history of poor night vision, bilateral atypical pigmentary changes of the retina, and degenerative changes in the vitreous humour. Additional diagnostic findings include retinoschisis, opaque retinal vessels, diffuse leakage from retinal capillaries, and cystoid macular oedema. Electroretinographic responses are either non-detectable or, if present, may show almost identical responses under both light- and dark-adapted conditions. In addition, highly abnormal flicker fusion frequency responses in the presence of relatively normal single-flash photopic amplitudes may be seen.

Summary

Extensive retinal vascular disease was noted in three patients from two families with Favre-Goldmann syndrome. In addition to classical features they had pronounced leakage from some retinal vessels. Vessels were either opaque ('sclerotic') or non-perfused. Cystoid macular oedema was a contributing cause of decreased vision. Two of the three patients showed a discrepancy on electroretinography between single-flash photopic amplitudes and flicker fusion frequency. This may be characteristic of Favre-Goldmann syndrome.

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Unilateral retinitis pigmentosa sine pigmento

JEROME T. PEARLMAN, JOAN SAXTON, AND GARY HOFFMAN
From the Department of Ophthalmology, Visual Physiology Laboratory, Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, USA
AND
STANLEY CARSON
From the Department of Ophthalmology, USC School of Medicine, Los Angeles, USA

At the Fourth ISCERG Symposium, held in Hakone, Japan, in 1966 Straub (1966) reviewed the subject of unilateral retinitis pigmentosa and made a number of important observations. Up to then only 34 cases of unilateral retinitis pigmentosa had been reported. Only one of them was of unilateral disease without pigment (Jacobson and Stephens, 1962). Rickers and Domarus (1974) stated that nearly 100 cases of unilateral retinitis pigmentosa had been described since the first report in 1865. They thought that the diagnosis could be verified in only about 20 cases.

Straub emphasized the clinical value of electroretinography (ERG) in establishing the truly unilateral nature of such cases, indicating that the ERG response must be normal in the unaffected eye. Others have long recognized that many cases of supposed unilateral retinitis pigmentosa were actually instances of highly asymmetric bilateral disease in which the 'normal' eye eventually showed the disorder, but only much later. Franceschetti, François, and Babel (1963) showed that the ERG response in such cases was impaired in both eyes. This significant clinical feature distinguishes genuine unilateral disease from 'pseudounilateral' (that is, asymmetric bilateral) retinitis pigmentosa.

Henkes (1964) found that the electro-oculogram was bilaterally disturbed in many instances of presumed unilateral retinitis pigmentosa but normal in the unaffected eye in truly unilateral cases. Thus measuring the resting potential of the eyes as well as the ERG is of value.

If unilateral retinitis pigmentosa is uncommon, cases without pigmentation are even rarer. We report here a case of unilateral retinitis pigmentosa sine pigmento.

Case report

A 27-year-old White woman was first seen at the Jules Stein Eye Institute on 7 March 1974 complaining of seeing spots before the left eye for the past three weeks. She was taking oral contraceptives, but otherwise her past medical history was normal. There was no family history of consanguinity. Childhood diseases included measles, mumps, and chicken pox. Her serology was normal. She did not complain of the right eye and of only minimal symptoms in the left. Unaided visual acuity was 20/20 in each eye, and she did not wear spectacles.

The findings on external examination were within normal limits. Slit-lamp examination showed nothing but a number of dot-like opacities in the anterior vitreous of the left (affected) eye. Initially, these dot-like opacities were thought to be evidence of an inflammatory aetiology of this condition. Such opacities, however, exist in the vitreous of patients with tapetoretinal degeneration (Berliner, 1949). Their absence in the unaffected eye was interpreted as additional evidence of the unilaterality of this patient's disorder.

Ophthalmoscopy

The fundus of each eye was examined through pupils dilated with 1 per cent tropicamide and 10 per cent viscous phenylephrine hydrochloride ophthalmic solutions (Fig. 1). The left eye showed some haziness of the vitreous; much attenuated retinal arterioles; and a subtle, patchy retinal pigment epithelial disturbance in the midperiphery. There was no convincing pallor of the left optic nerve head. The right fundus was normal. No pigmentary changes of salt and pepper or bone corpuscle type were noted. Intraocular pressure by applanation tonometry was 16 mmHg on each side. Special tests consisted of fluorescein angiography, Kodachrome fundus photography, colour vision tests, Goldmann fields, dark adaptometry, electroretinography, and electro-oculography.

Fluorescein angiography of the left eye showed a significant delay in the appearance of dye in the vascular tree relative to the right eye, with considerable attenuation of the retinal arterioles. Even the veins were of smaller calibre. Compared with the right eye, there was a striking hyperfluorescence on the left side in the late

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Address for reprints: Jerome T. Pearlman, MD, Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, California 90024

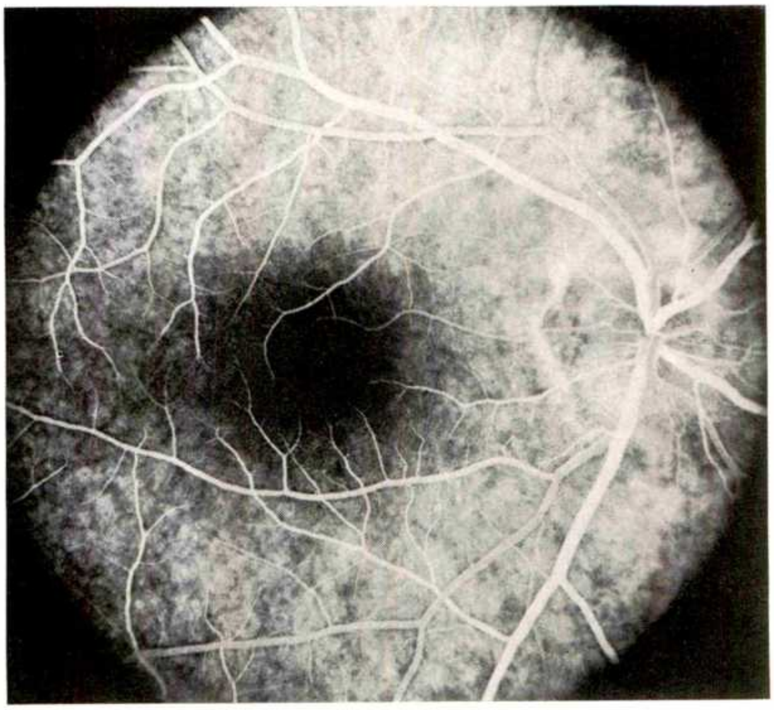
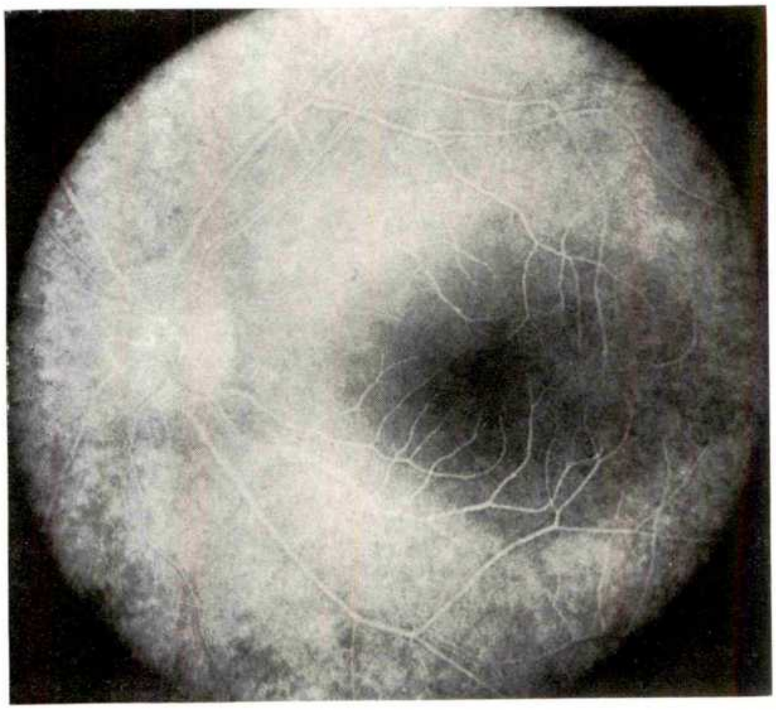


FIG. 2 *Fluorescein fundus angiograms*

(a) *Normal right eye 25 seconds after injection of dye*



(b) *Abnormal left eye 23·8 seconds after injection of dye. Note unusual degree of choroidal hyperfluorescence surrounding darker, central macular area, indicating diffuse abnormality of retinal pigment epithelial layer*

phase. No macular disturbance was noted, even on magnification. Fixation was normal (Fig. 2*b*). A similar study of the right eye showed a normal transit and late phase (Fig. 2*a*).

Colour vision was normal in both eyes when tested with AO H-R-R and Ishihara pseudoisochromatic plates. No mistakes were made. Goldmann fields of the right eye were within normal limits; those of the

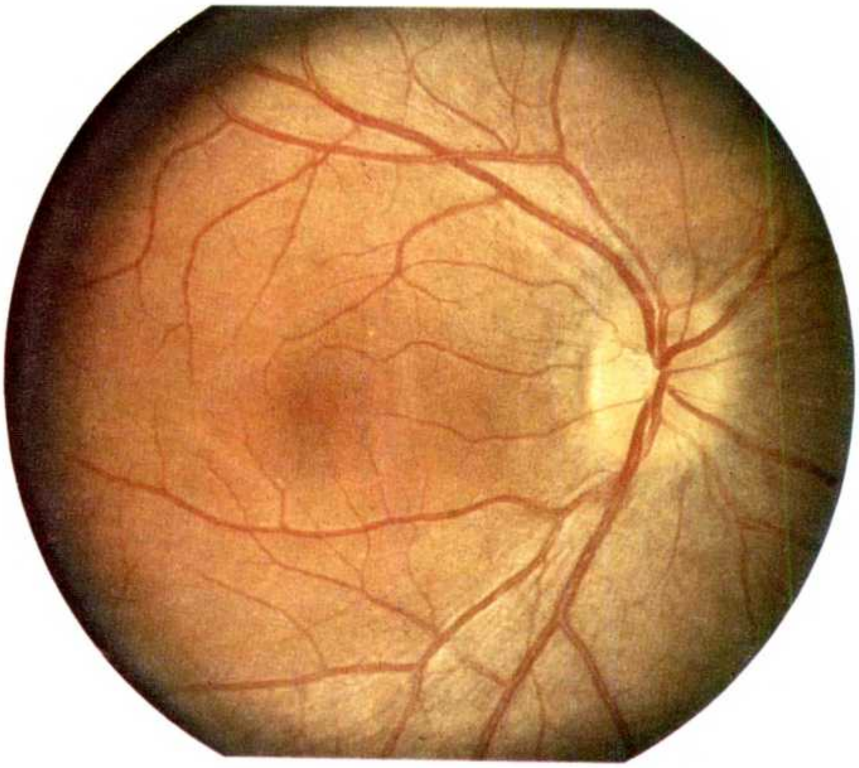
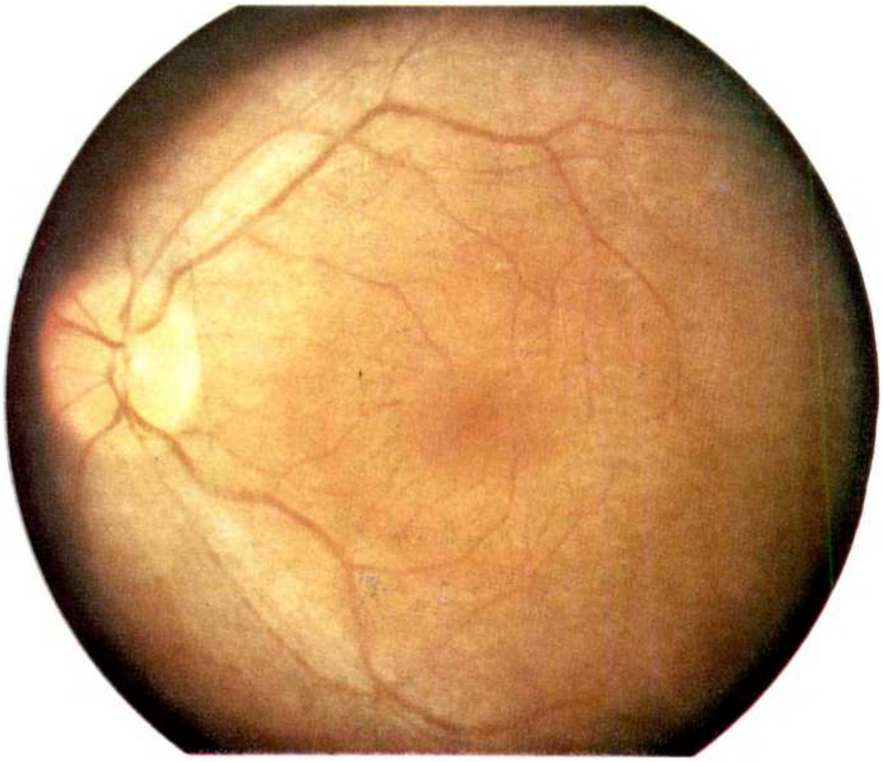
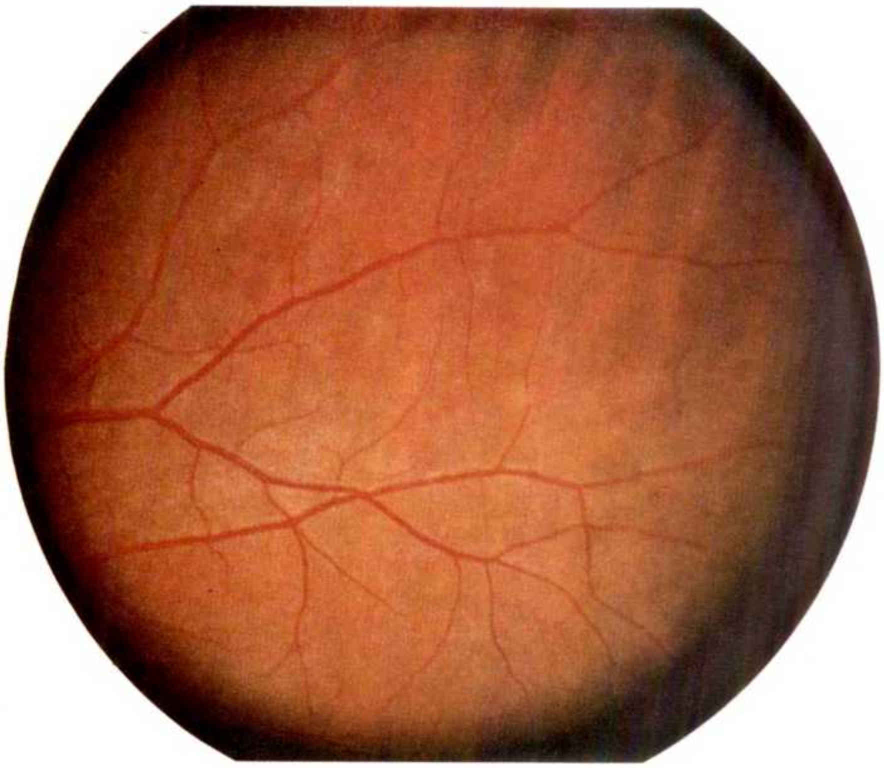


FIG. 1 *Fundus photographs*

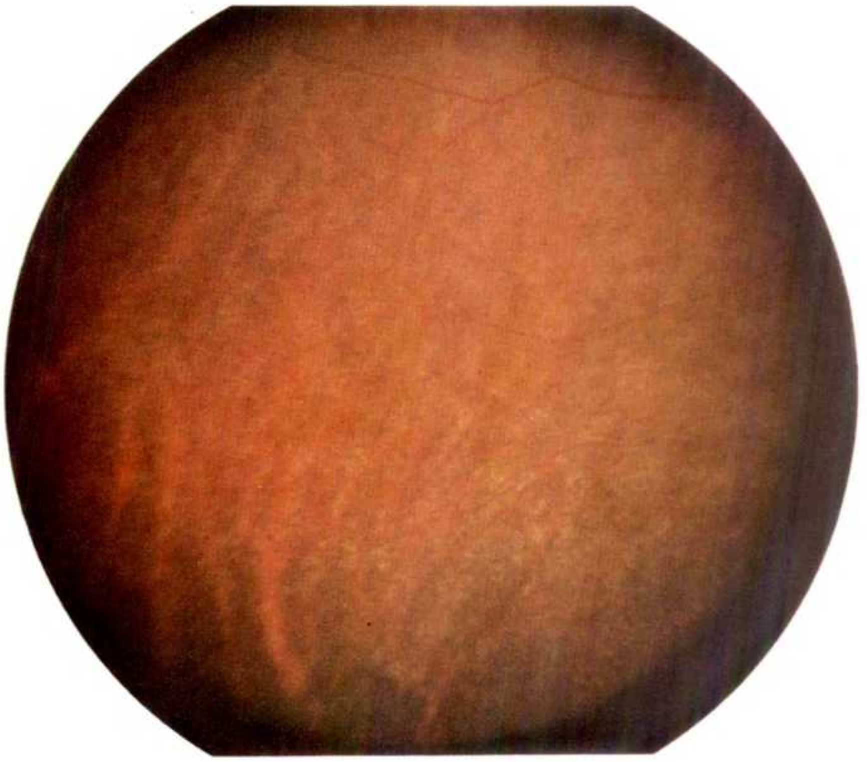
(a) *Disc and macula of normal right eye*



(b) *Disc and macula of affected left eye. Note absence of significant optic nerve pallor and presence of much attenuated retinal arterioles*



(c) *Periphery of normal right eye*



(d) *Periphery of abnormal left eye showing mottling in retinal pigment epithelial layer. No bone corpuscular pigment was seen anywhere in left fundus*

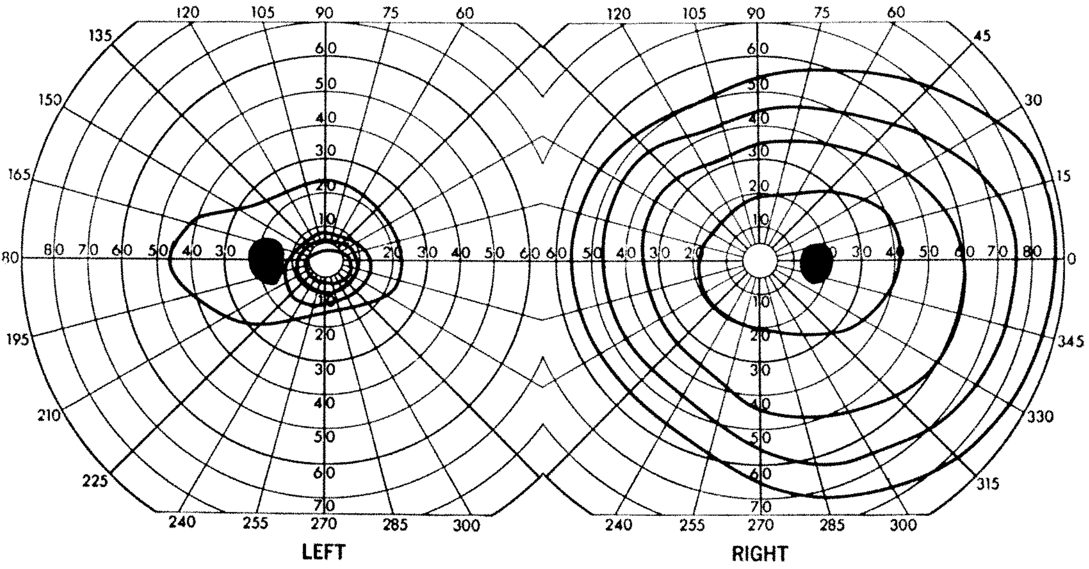


FIG. 3 *Goldmann fields of normal right eye and abnormal left eye. Note constriction of all isoptres in OS and the absence of central scotoma. Largest isoptre is IV-4; next is 1–4; next is 1–3; and smallest 1–2 on the Goldmann perimeter*

left eye showed pronounced constriction of the peripheral field compared with the right. The I-2 isoptre of the left eye was reduced to about six degrees (Fig. 3).

Dark-adaptation studies

Dark-adaptation studies were made with the Goldmann-Weekers adaptometer with a one degree test object flickering on and off at one-second dark and light intervals. The test spot was located 5·5 cm below the fixation point on the instrument, and thus projected 11 degrees above the fovea on the subject's retina. Each test was conducted in the standard manner with pupils dilated by tropicamide 1 per cent and phenylephrine hydrochloride 10 per cent viscous ophthalmic solutions. The subject was exposed to pre-adapting illumination of 18 lux (2800 abs) for five minutes. Each test lasted a total of 45 minutes. The tracings showed a normal cone onset for both eyes and a normal development of the rod portion of the curve for the right eye. The left eye showed an abnormal rod development and a raised threshold, beginning at about nine minutes and persisting for the duration of the test. At the end of the examination the final rod threshold for the left eye was 1·3 log units higher than that of the right eye (Fig. 4).

Electroretinography

ERG studies were made in the routine manner of our laboratory. After dark adaptometry patients dark-adapted for an additional 45 minutes. Burian-Allen contact lens electrodes were inserted under red light illumination after instilling proparacaine hydrochloride 0·05 per cent ophthalmic solution for corneal anaesthesia. White light stimuli of 20 ms duration recorded single and multiple flash responses. Dark-adapted eyes placed in Maxwellian view received the flashes via optical fibres from a tungsten lamp, with a Hartline shutter and a series of neutral density filters to vary stimulus intensity. Threshold responses were measured, beginning with subthreshold stimuli in single flashes. After about 30 seconds the next flash was presented. As the stimulus intensity increased the interval between single flashes was lengthened to about one minute to ensure the dark-adapted state. The intensity of the stimulus light was such as to generate a maximal b-wave; the same light was used for both eyes, which were always recorded simultaneously. The patient's tracings showed normal b-waves on the right side and a highly abnormal, but barely recordable b-wave response on the left side (Fig. 5).

Electro-oculography

Electro-oculography was performed with the patient sitting in a darkened room for 45 minutes. Skin electrodes were attached at the medial and lateral canthi of each eye and in the centre of the forehead. A baseline response was recorded after one hour of dark adaptation. Each channel of the recording instrument was calibrated at 400 μV. The dark-adapted response was next measured for 12·5 minutes. With the eyes executing an excursion of 20 degrees at a distance of 1·82 m from fixation targets the amplitude of the dark response was 1000 μV for the right eye and 600 μV for the left. Next, the light-adapted response was measured for 12·5 minutes. The 9 minutes reading was the maximum light rise. The normal right eye showed excursion amplitudes of 2200 μV while the abnormal left eye showed the same amplitude, or no 'light rise' at all. Thus the Arden light-to-dark ratio of the normal right eye was 2·2, or 220 per cent, while the abnormal left eye showed a

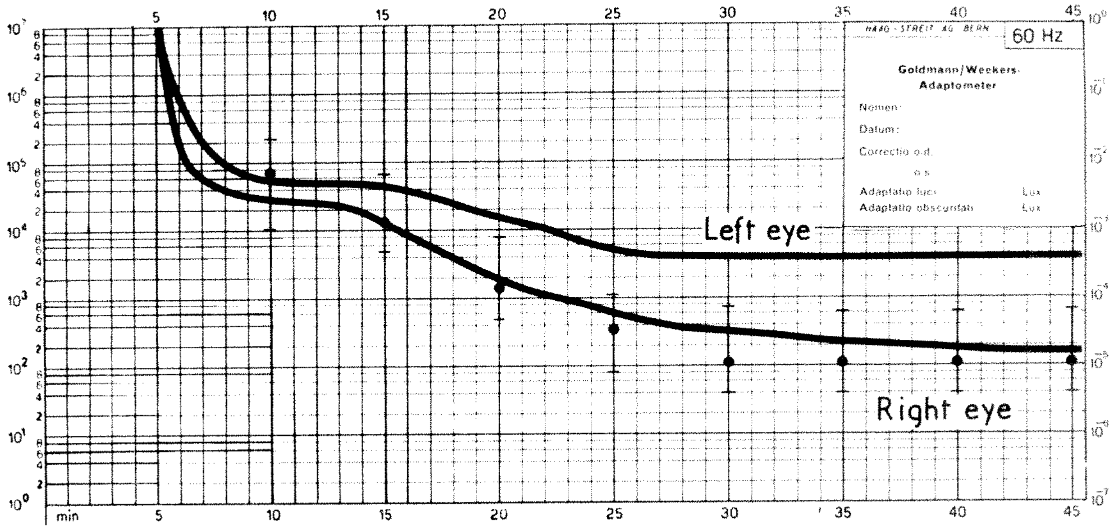


FIG. 4 *Dark adaptation record showing raised threshold of the left eye compared with normal threshold of right eye. Difference of 1·3 log units in threshold indicates 50-fold decrease in sensitivity of left eye. Initial cone portions of two curves (between 5 and 8 min) were very similar. Dots and bars indicate normal mean (±2 SD) values for test in our laboratory*

ratio of 1·0 or 100 per cent (Fig. 6). The EOG has been performed four times during the past 18 months. Since different instruments and protocols were used it is impossible to compare precisely the several tests, except to confirm the constant abnormality of the left eye as opposed to the normal right eye. The right eye has shown no evidence of functional impairment since our first contact with the patient.

Discussion

The diagnosis of retinitis pigmentosa sine pigmento from purely ophthalmoscopic findings is rather more difficult than in the more typical case of the disease with pigment deposition. Indeed, changes in the retinal pigment epithelial layer in the absence of pigment deposition are remarkably subtle and may easily escape detection. Optic pallor may be minimal or absent, as in this patient. Arteriolar attenuation was obvious in our case but may not be so in every case. Moreover, when evaluating the significance of arteriolar attenuation the possibility of a previous central retinal artery occlusion must be considered. This condition, we thought, could be ruled out in our case because of the patient's young age and the absence of any history of sudden, severe loss of vision on the affected side. Thus monocular constriction of the peripheral field in the presence of ipsilateral nightblindness may be the first diagnostic clue. Next, the finding of a grossly diminished b-wave or non-recordable ERG response on the one side and a normal response on the other lends additional weight to the impression of retinitis pigmentosa sine pigmento. And, finally, a unilaterally abnormal EOG supports the diagnosis even more strongly.

The amount of pigmentation in retinitis pigmentosa is variable. Pigment deposition can be sparse, moderate, or heavy—depending on any number of factors, including the patient's age, duration of the disease, and an individual proclivity, as it were, to deposit intraretinal pigment. Quite likely the sine pigmento state is one extreme of a wide spectrum of pigmentary patterns found in that group of diseases called 'retinitis pigmentosa' and not the manifestation of a separate or distinct

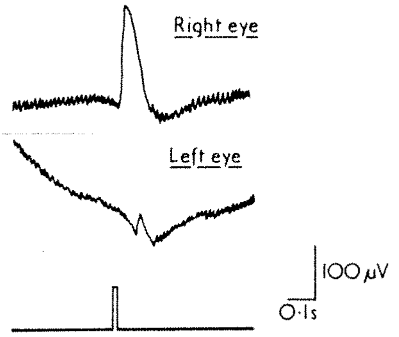


FIG. 5 *Electroretinographic record of single flash simultaneously received by right eye (top) and left eye (bottom). Intensity used was equal for both eyes. Normal right eye shows small a-wave and large b-wave; affected left eye shows severely impaired b-wave*

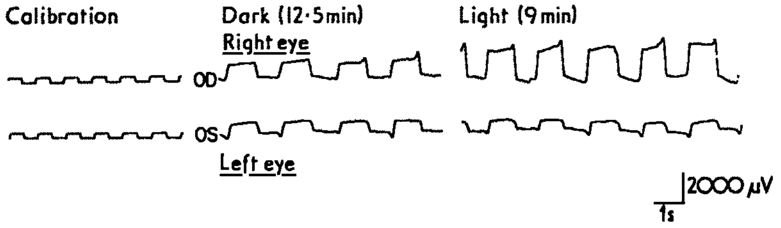


FIG. 6 *Electro-oculographic response of both eyes after 12·5 minutes of dark adaptation and 9 minutes of light adaptation. Unaffected right eye shows normal light rise of over 200 per cent while involved left eye shows no light rise whatever*

disorder. Our patient has been followed-up since March 1974 and still shows normal retinal function on the right side, but there is no guarantee that at some future time she may not develop bilateral disease or develop pigmentation on the currently affected side. Nevertheless, for the present the patient may be reasonably classified as an example of unilateral retinitis pigmentosa without pigment because all diagnostic criteria have been met.

Summary

A patient presented with unilateral findings of night blindness shown by impaired rod function and dark adaptation, constricted visual fields with good central acuity, a barely recordable electro-retinographic b-wave, and a unilaterally impaired electro-oculogram. There were none of the pigmentary changes usually associated with retinitis pigmentosa. The unaffected right eye was normal in all respects. Therefore the case is most probably one of unilateral retinitis pigmentosa sine pigmento.

We thank Mrs Nola J. Allston and Mr Robert Petrus for their technical assistance.

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Ocular findings in elderly cases of homozygous sickle-cell disease in Jamaica

P. I. CONDON* AND G. R. SERJEANT
From the MRC Laboratories (Jamaica), University of the West Indies, Kingston, Jamaica

Sickle-cell disease is characterized by recurrent vascular occlusive episodes and a progressive obliteration of capillary beds. This process can be directly observed in the eye and its occurrence in the peripheral retina has been well documented (Welch and Goldberg, 1966; Goldberg, 1971; Condon and Serjeant, 1972a, b, c). The effects of such thrombotic episodes might be expected to accumulate with age and to be most marked in elderly patients. The results of ocular examinations in 60 patients aged over 40 years with homozygous sickle-cell (SS) disease in Jamaica are presented below.

Patients and methods

The patients attended the sickle-cell clinic of the University Hospital of the West Indies. Ocular examination of 56 out of 66 patients aged over 40 years (born before 1 January 1935) attending the clinic was possible. In addition, the cases of four patients (cases 2, 31, 47, 54) aged over 40 years at the time of previous examinations, but who had since died, were studied. The overall group therefore consisted of 60 patients (27 men, 33 women) whose ages ranged from 40–66 years.

Homozygous sickle-cell disease was diagnosed on criteria reported elsewhere (Serjeant, 1974). Methods of ocular examination have been previously described (Condon and Serjeant, 1972a). Retinitis proliferans and angioid streaks were confirmed in each case by fluorescein angiography.

Results

The findings are summarized in Table I. Visual acuity was decreased in 40 eyes (25 patients) and was 6/60 or less in eight eyes (eight patients). The causes included astigmatic refractive errors in four patients, trauma in three, retinal detachment in two, macular degeneration of unknown origin in seven, a toxoplasma lesion, long-standing optic atrophy, cataracts, and vitreous haemorrhage in one each, and was unknown in five patients. Traumatic causes were more common in younger patients and macular degeneration more common in the older group.

Tortuosity of the major retinal vessels was present in 18 (30 per cent) patients affecting the veins alone in 13 and the arteries and veins in five. Peripheral retinal vessel disease was classified as previously described (Condon and Serjeant, 1972a) into three grades. Grade I consisted of narrowing of peripheral arterioles with tortuosity and abnormal looping of peripheral venules. Grade II included tortuosity, dilatation, and microaneurysmal formation in the peripheral capillary network; coarsening of the network with loss of some fine vessels; and abnormal branching of peripheral venules. Grade III changes were arteriolar occlusions. The grade of vessel disease was usually identical in both eyes (37 patients), although differences between eyes of one grade (12 patients) or even two grades (six patients) did occur. Grade I changes were present in 40 eyes, grade II in 21, and grade III in 40. The peripheral retinal vessels appeared normal in 15 eyes. Arterio-venous fistulae occurred in four eyes (four patients) and was associated with grade III vessel disease in all cases. Retinitis proliferans occurred in 12 eyes (eight patients), the lesions being often multiple and affecting large areas of the peripheral retina. In four of the eight patients the lesions had fibrosed, presumably after spontaneous vessel occlusion.

In order to assess the effect of age on peripheral retinal vessel disease and retinitis proliferans the group was divided into those aged 45 years or under (29 patients) and those aged 46 years or over (31 patients). The results are summarized in Table II, which shows that mild grades of vessel disease (I and II) were more common in the younger groups and that the more severe grade III and retinitis proliferans predominated in the older group. Women also seemed to have more normal retinal vasculature and accounted for 5/7 (71 per cent) patients with normal vessels and 12/14 (86 per cent) of those with grade I vessel disease.

Chorioretinal scars known as 'sunburst' spots

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*Present address: Regional Eye Department, Ardkeen Hospital, Waterford, Ireland

Address for reprints: Ardkeen Hospital, Waterford, Ireland

Table I *Ocular findings in 60 patients aged 40 or over with homozygous sickle-cell disease. Arabic figures refer to number of lesions in eye. See text for criteria for grading retinal vessel disease*

Case no.	*Age and sex*	*Visual acuity*		*Tortuous major retinal vessels (A=arterial, V=venous)*	*Grade of retinal vessel disease*		*Arterio-venous fistulae*		*Retinitis proliferans*		*Chorio-retinal sunburst lesions*		*Micro-aneurysms of posterior pole*		*Angioid streaks*		*Comments*
		R	*L*		*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	
1	40 M	6/6	6/6	—	II	II	—	—	—	—	2	—	—	—	—	—	
2	40 M	6/6	6/60	—	II	II	—	—	—	—	—	—	—	—	—	—	(L) long-standing optic atrophy
3	40 F	6/6	6/6	V	I	I	—	—	—	—	—	—	—	+	—	—	
4	41 M	6/6	6/6	—	III	I	—	—	—	—	—	—	—	—	—	—	
5	41 M	6/6	6/6	AV	II	II	—	—	—	—	—	—	—	—	—	—	
6	41 M	6/6	1/60	V	III	—*	—	—*	—	—*	—	—*	—	—	—	—	Traumatic maculopathy
7	41 M	6/6	6/6	—	—	—	—	—	—	—	—	—	—	—	—	—	
8	41 F	6/6	6/6	—	III	III	—	—	—	—	—	—	—	—	—	—	
9	42 M	HM	6/6	V	—*	III	—*	—	—*	—	—*	—	—	—	—	—	Traumatic lesion (R) eye
10	42 M	6/6	6/6	V	I	I	—	—	—	—	—	—	—	—	—	—	
11	42 M	6/6	6/6	V	III	II	1	—	—	—	—	—	—	—	+	—	
12	42 F	6/6	6/6	—	I	III	—	—	—	—	3	1	—	—	—	—	
13	42 F	6/9	6/12	—	I	I	—	—	—	—	—	—	—	—	—	—	Myopic astigmatism
14	42 F	6/6	6/6	—	I	III	—	—	—	—	—	—	—	—	—	—	
15	42 F	6/6	6/6	—	II	I	—	—	—	—	—	—	—	+	—	—	
16	43 M	6/6	6/6	—	—	II	—	—	—	—	1	1	—	—	—	—	
17	43 M	6/6	6/6	—	III	III	—	—	—	—	1	—	+	+	—	—	
18	43 M	6/18	6/24	—	II	III	—	—	—	—	—	1	++	++	—	—	
19	43 M	6/36	6/6	—	—	—	—	—	—	—	—	—	—	—	+	++	Healed toxoplasma lesion (R) macula
20	43 M	6/6	6/6	—	II	II	—	—	—	—	1	—	++	++	+	++	
21	43 F	6/6	6/6	V	I	I	—	—	—	—	—	—	—	—	—	—	
22	44 F	6/6	6/6	—	I	I	—	—	—	—	—	—	—	—	—	—	
23	44 F	6/6	6/6	V	I	I	—	—	—	—	—	—	—	—	—	—	
24	44 F	6/6	CF	—	I	I	—	—	—	—	—	—	—	—	—	—	Traumatic lesion (L) eye
25	44 F	6/6	6/6	V	III	III	—	1	2	1	—	1	—	—	—	—	
26	44 F	6/6	6/6	—	—	—	—	—	—	—	—	—	—	—	—	—	
27	45 F	6/6	6/6	—	III	II	—	—	—	—	—	—	—	—	—	—	
28	45 M	6/6	6/6	—	I	I	—	—	—	—	—	—	—	—	+++	++	
29	45 F	6/6	6/9	V	I	I	—	—	—	—	—	—	—	—	—	—	Macular degeneration
30	46 M	6/12	6/12	—	III	III	—	—	—	—	1	—	—	+	++	+	
31	46 M	6/6	6/6	—	II	I	—	—	—	—	—	—	—	—	—	—	
32	46 F	6/12	6/6	—	II	I	—	—	—	—	1	1	—	—	—	—	Macular degeneration
33	46 F	6/6	6/6	—	I	I	—	—	—	—	—	—	—	—	—	—	
34	47 M	6/12	6/12	V	II	I	—	—	—	—	—	1	—	+	—	—	Macular degeneration
35	47 F	6/6	6/6	—	II	III	—	—	—	—	—	—	—	—	++	+	
36	48 M	6/12	6/9	—	III	I	—	—	—	—	1	1	—	—	—	—	
37	48 F	6/9	6/9	—	I	I	—	—	—	—	—	—	—	—	—	—	
38	49 M	6/6	6/6	—	III	III	—	—	9	3	—	1	—	—	—	—	
39	49 M	6/6	6/6	—	III	III	2	—	2	1	1	—	—	—	++	+	
40	49 M	6/6	6/6	—	I	III	—	—	—	—	—	—	—	—	—	—	
41	49 F	6/6	6/6	—	I	I	—	—	—	—	—	—	—	—	—	—	
42	49 F	6/6	6/6	AV	—	—	—	—	—	—	—	—	—	—	—	—	
43	49 F	6/18	6/18	—	I	I	—	—	—	—	—	—	—	—	—	—	Macular degeneration
44	50 M	Nil	6/12	—	—*	III	—*	1	—*	3	—*	1	—*	+	—*	—	?Retinal detachment (R)
45	53 M	6/6	6/6	V	II	I	—	—	—	—	—	—	—	—	++	+	
46	53 F	6/9	6/9	—	II	III	—	—	—	—	—	2	—	—	—	—	
47	53 F	6/18	6/12	—	II	III	—	—	—	1	—	—	—	—	—	—	Macular degeneration
48	55 F	6/12	6/12	V	II	I	—	—	—	—	—	—	—	—	—	—	Myopic astigmatism
49	55 F	6/6	6/6	—	I	I	—	—	—	—	—	—	—	—	++	+	
50	56 F	6/6	6/24	AV	III	III	—	—	2	3	—	—	—	—	—	—	(L) perimacular fibrosis from vitreous haemorrhage
51	57 F	6/6	6/6	—	III	III	—	—	—	—	1	—	—	—	—	—	
52	58 F	6/24	6/6	—	III	III	—	—	—	—	—	—	—	—	++	+	Amblyopia
53	59 F	6/6	Nil	—	III	—*	—	—*	6	—*	—	—*	—	—*	—	—*	Retinal detachment (L)
54	59 F	6/36	2/60	—	I	III	—	—	—	—	—	—	—	—	—	—	Senile macular degeneration and cataracts
55	59 F	6/12	6/24	AV	III	III	—	—	—	4	—	—	—	—	++	+	(L) vitreous haemorrhage
56	60 M	6/6	6/6	—	III	III	—	—	—	—	—	—	—	—	++	+	
57	60 F	6/36	6/24	AV	—	—	—	—	—	—	—	—	—	—	++	+	Macular degeneration
58	60 F	6/6	6/6	—	—	—	—	—	—	—	—	—	—	—	—	—	
59	61 F	6/36	6/60	—	—	—	—	—	—	—	—	—	—	—	—	—	Senile cataracts
60	66 M	6/6	6/6	V	III	III	—	—	—	—	—	—	—	+	—	—	

*Inapplicable: peripheral retina could not be seen
Severity of lesion: +, ++, +++

Table II *Age distribution of peripheral retinal vessel disease and retinitis proliferans*

Age (years)	*No.*	*Eyes observed**	*Eyes affected*									
			Normal vessels		*Grade of vessel disease*						*RP*	
					I		*II*		*III*			
			No.	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*
40–45	29	56	7	12	22	38	13	22	14	24	1	2
46–60	31	60	8	13	18	29	8	13	26	42	7	11

*Excludes four eyes in which assessment of the peripheral retina was impossible

occurred in 20 eyes (16 patients). Microaneurysms at the posterior pole were seen in 12 eyes (nine patients). Angioid streaks occurred in 25 eyes (13 patients). They were bilateral in 12 patients, in 11 of whom they were better developed on the right side. They occurred in 4/29 (14 per cent) patients aged 45 years and under compared to 9/33 (27 per cent) patients over this age. In one case (Case 20) angioid streaks developed over a four-year period of observation between ages 39–43. In another patient (Case 57) bilateral macular degeneration and reduced visual acuity occurred concurrently with early angioid streaks around the disc, but fluorescein angiography suggested that these lesions were probably unassociated. Clinical evidence of pseudoxanthoma elasticum was not present in any patient with angioid streaks.

Discussion

Tortuosity of the major retinal veins has been reported in homozygous sickle-cell disease in between 10–96 per cent of cases (Klinefelter, 1942; Henry and Chapman, 1954; Smith and Conley, 1954; Hannon, 1956; Hook and Cooper, 1958; Lieb, Geeraets, and Guerry, 1959; Welch and Goldberg, 1966). Condon and Serjeant (1972a) noted this finding in 8/76 (11 per cent) patients with SS disease in an earlier report and in 18/60 (30 per cent) of the present series. The variable prevalence of this sign may reflect real differences in populations or may result from the subjective nature of tortuosity. Interpretation of this finding is further complicated by lack of valid control data. However, the available evidence suggests that tortuosity of the major retinal veins is associated with sickle-cell disease. Tortuosity of both arteries and veins may indicate an independently inherited genetically determined abnormality which can also coincide with sickle-cell disease (Condon and Serjeant, 1972a).

Although the severity of peripheral retinal vessel disease generally increased with age, some elderly patients still manifested normal vessels or very mild changes. Arterio-venous fistulae, which are presumed to precede the development of retinitis proliferans, occurred mainly in the younger patients, whereas retinitis proliferans (RP) was almost confined to older patients of the series. The relatively high prevalence of RP in patients over the age of 50 (29 per cent) is of especial interest since this complication has been considered uncommon in other series of patients with SS disease (Henry and Chapman, 1954; Lieb and others, 1959; Welch and Goldberg, 1966). In an earlier series that included Jamaican patients of all ages Condon and Serjeant (1972a) found this complication in only 2/76 (3 per cent) patients, one aged 34 and the other aged 55 (case 53 in present report). Since RP seems to be age-related, some variation in prevalence may reflect different age structures of other series. It was of interest that in 4/8 patients areas of retinitis proliferans had become spontaneously occluded and the vessels no longer leaked fluorescein on angiography. Although spontaneous obliteration of new vessels constitutes a progression of vascular disease in pathological terms, such a process would tend to halt the progressive nature of peripheral retinal ischaemia and render less likely complications such as vitreous haemorrhage and retinal detachment.

The aetiology of pigmented chorioretinal lesions, or 'sunburst' spots, is unknown although they may result from retinal or choroidal infarcts. This concept was supported by the presence of these lesions in 11/40 (28 per cent) eyes with grade III vessel disease compared with 9/76 (12 per cent) with milder grades of vessel disease.

Tortuosity and dilatation of the capillary network with microaneurysmal formation at the posterior pole was noted by Lieb and others (1959) and reported in 30/76 (40 per cent) patients with SS disease in Jamaica (Condon and Serjeant, 1972a). This finding appears more characteristic of homozygous sickle cell disease than of other variants such as sickle-cell-haemoglobin C disease and sickle-cell-β thalassaemia (Condon and Serjeant, 1972b, c), and it is tempting to postulate that they are a retinal equivalent to the abnormal dilatations often seen in the conjunctival capillary bed (Serjeant, Condon, and Serjeant, 1972).

Angioid streaks are a recognized feature of sickle-cell retinopathy, although case reports are limited to a few patients. Paton (1959) and Lieb and others (1959) each described two cases with SS disease. Geeraets and Guerry (1960) reported five cases, three with probable SS disease and two with SC disease. Suerig and Siefert (1964) described a single case with SS disease, and Condon and Serjeant (1972b) reported a single case with SC disease. In two of these reports pseudoxanthoma elasticum was also present, but in the other nine cases the angioid streaks were attributed to sickle-cell disease. In view of these sparse case reports the finding of angioid streaks in 13/60 (22 per cent) patients in the present series is of especial interest and compares with an incidence of 3/150 (2 per cent) in younger Jamaican patients (affected cases aged 25, 27, and 32 respectively). Angioid streaks increased in frequency with age in sickle-cell disease and they have developed in two patients aged 25 and 43 in the Jamaican group.

Angioid streaks are characterized histologically by defects in Bruch's membrane, and most cases have been associated with either pseudoxanthoma elasticum or osteitis deformans (Paget's disease). The aetiology of angioid streaks in SS disease is unknown. Paton (1959) suggested that vascular obstructions affected the chorio-capillary circulation, whereas Geeraets and Guerry (1960) thought the cause could be an avascular degeneration of elastic tissue consequent on involvement of the posterior ciliary vessels. In this context it is of interest that three patients with evidence of posterior ciliary vessel obstruction developed segmented chorioretinal atrophies, but failed to show any evidence of angioid streaks (Condon, Serjeant, and Ikeda, 1973). The clinical course of angioid streaks in sickle-cell disease seems more benign than when associated with other conditions. No associated haemorrhages or exudates were seen in the present group, and in the one case with macular degeneration fluorescein angiography suggested that the two lesions may have been coincidental.

In summary, a distinctive pattern of ocular pathology emerges from the present elderly group. Severe grades of peripheral retinal vessel disease are common, and the incidence of retinitis proliferans and of angioid streaks is high, especially in those patients over 50 years of age. Some patients are exceptions to this general pattern and have only mild retinal vascular changes despite relatively advanced age. These exceptions could be of great interest and may represent variations of homozygous sickle-cell disease in which the tendency to vessel obstruction is much diminished.

Summary

The ocular findings in 60 patients with homozygous sickle-cell disease over the age of 40 years have been described. Peripheral retinal vessel disease was common and appeared to increase with age. Retinitis proliferans was common among older patients in the group. Angioid streaks occurred in 13 (22 per cent) patients.

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Brit. J. Ophthal. (1976) **60**, 365

Ocular toxocariasis in adults

E. R. RAISTRICK AND J. C. DEAN HART
From the Department of Ophthalmology, Bristol Eye Hospital, Bristol

The larva of the nematode *Toxocara canis* was first identified as a cause of intraocular disease by Nichols (1956). Subsequent studies showed that it may produce a variety of ocular lesions, including localized retinal granulomata (Ashton, 1960), endophthalmitis (Irvine and Irvine, 1959; Duguid, 1961a), or papillitis (Bird, Smith, and Curtin, 1970). Nearly all the reported cases are of ocular lesions in children (Wilkinson and Welch, 1971), and the inference has been that the unhygienic habits of infants coming into contact with infected dogs, or soil contaminated with the ova of the nematode, is a major factor in limiting ocular disease to the young (Duguid, 1961b; Unsworth, Fox, Rosenthal, and Shelton, 1965). However, the proportion of the population with antibodies to *Toxocara* species increases with age. In a study of healthy blood donors in the age group 18–25 years toxocaral fluorescent antibody tests were positive in 4·5 per cent and this figure rose to 7·1 per cent in the 30–40 age group (Woodruff, 1973). Clearly adult toxocaral infection also occurs.

Clinical reports of retinal lesions in adults due to presumed toxocaral infection are few. Phillips and MacKenzie (1973) described the case of a 25-year-old woman who presented with a history of recent uniocular visual deterioration and was found to have a right papillitis. Initial toxocaral fluorescent antibody tests were negative, but later they were positive. More recently, another case was reported of a 50-year-old man who developed moderate deterioration of vision in his right eye after a short febrile illness. He had a right pigment epithelial detachment adjacent to the macula and a linear opacity in the centre of the lesion changed its orientation over a period of days. He had a transient eosinophilia and toxocaral fluorescent antibody tests were positive (Raistrick and Dean Hart, 1975).

In this paper the ocular findings in three patients in the age group 20–29 years who complained of relatively sudden uniocular visual loss are described. All had posterior polar retinal lesions in the affected eyes, and ophthalmoscopic findings closely resembled those of proved toxocaral granulomata in children (Ashton, 1960). In all cases the toxocaral fluorescent antibody tests were positive.

Case reports

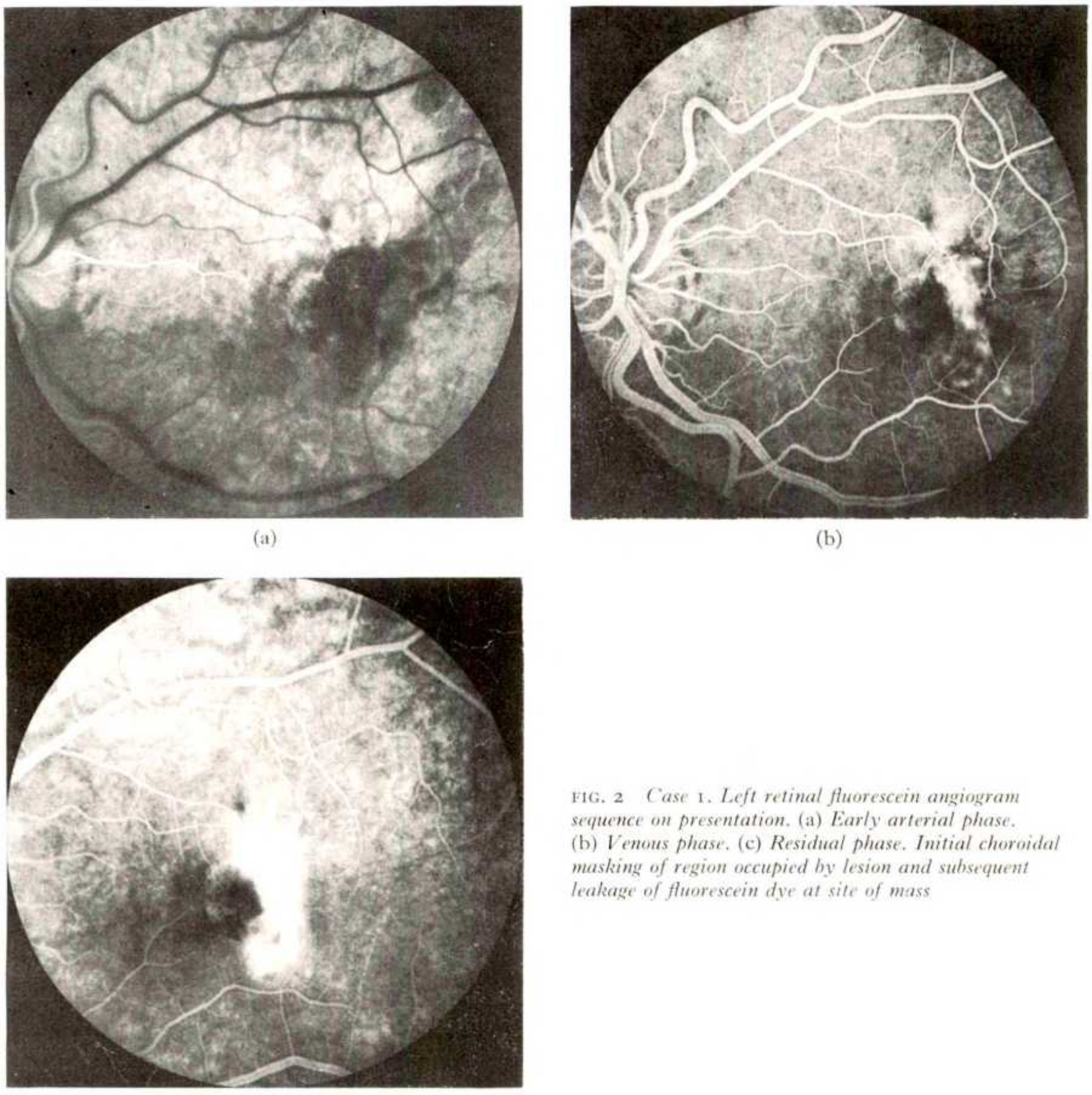
CASE 1

A 20-year-old woman secretary with a record of good health complained in June 1972 of deteriorating vision in the left eye over a period of four weeks and intermittent, left-sided frontal headaches. Her corrected visual acuities were 6/5 right and less than 6/60 left. The right eye was normal on biomicroscopy and ophthalmoscopy, but in the fundus of the left eye there was a raised pigmented lesion involving the macula. Near to it were a few small, deep retinal haemorrhages and the surrounding retina appeared oedematous (Fig. 1*a*). There was a dense central scotoma of the left eye. *X*-ray examination of chest and skull showed no abnormalities and an ESR, a full blood count, and a dye test for toxoplasma were all within normal limits. No diagnosis was made and therefore no treatment instituted. Five months later the vision had improved spontaneously to 6/12 in the affected eye, though the retinal lesion appeared to be somewhat more extensive.

In January 1973 the left vision had fallen to 6/18 and the patient was admitted to hospital for further assessment. A general physical examination showed no positive findings. A short trial of systemic corticosteroid therapy failed to ameliorate her symptoms and her vision continued to deteriorate. Some nine months later the left acuity was reduced to counting fingers and the lesion now appeared as a raised white opaque, umbilicated swelling with clearly defined edges. A previously noted retinal blood vessel that crossed over the margin of the mass and dipped into the depressed central area had become grossly dilated (Fig. 1*b*). As the lesion on ophthalmoscopic examination closely resembled an illustration of toxocaral granuloma in a child described by Ashton (1960) we performed a toxocaral fluorescent antibody test. This was positive. On subsequent questioning the patient admitted close contact with a dog a few months before the onset of the symptoms.

In November 1974 the retinal lesion had flattened somewhat and the engorged blood vessel returned to its original calibre (Fig. 1*c*). Six months later the patient's central vision remained grossly impaired, but the lesion involving the macula was much flatter. Surrounding pigmentary changes were now obvious. Seven

Address for reprints: Mr J. C. Dean Hart, Bristol Eye Hospital, Bristol BS1 2LX



(a)

(b)

(c)

FIG. 2 *Case 1. Left retinal fluorescein angiogram sequence on presentation.* (a) *Early arterial phase.* (b) *Venous phase.* (c) *Residual phase. Initial choroidal masking of region occupied by lesion and subsequent leakage of fluorescein dye at site of mass*

months afterwards there was retinal scarring involving the macula with further progression of pigmentary disturbances at the posterior pole (Fig. 1*d*).

Fluorescein angiography

Fluorescein angiography soon after the patient was first seen showed, in the initial part of the dye transit, masking of the choroidal fluorescence at the site of the pigmented lesion with no abnormality of the overlying retinal vessels. In the venous and late phases there was progressive uptake of dye in the central area of the mass (Fig. 2*a*, *b*, *c*). Angiograms repeated in December 1975 showed changes associated with pigment epithelial clumping and atrophy localized to the posterior pole (Fig. 3*a*, *b*) with minimal uptake or leakage of dye.

CASE 2

A 25-year-old man, a driver, was referred in August 1973 with a few weeks' history of intermittent right-sided frontal headaches, occurring mostly in the evenings, and a progressive loss of central vision in his right eye. There was no history of general symptoms and his medical history was unremarkable. His left visual acuity was 6/4 and the right was reduced to counting fingers. The left eye showed no abnormal features, but ophthalmoscopy of the right fundus

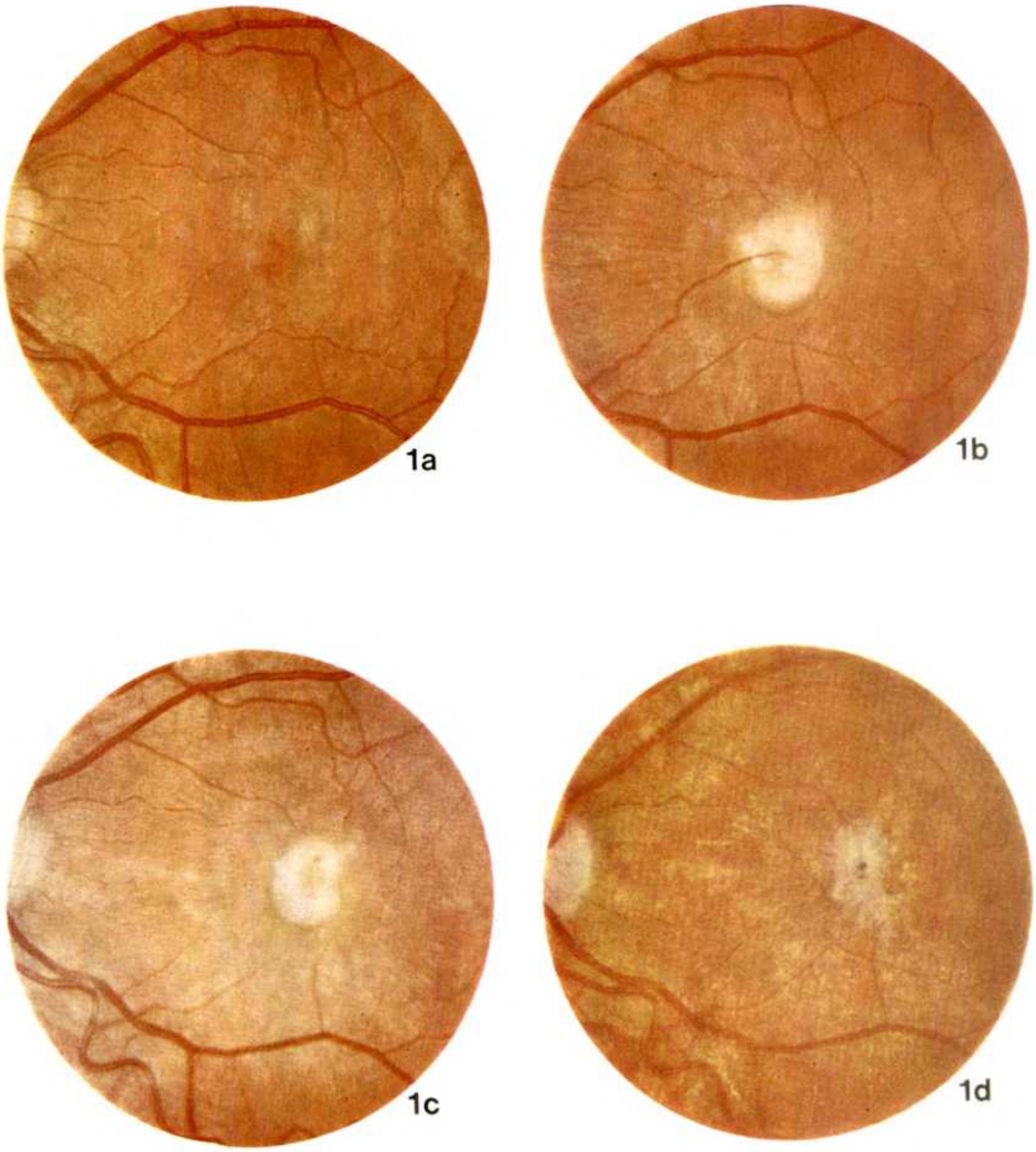
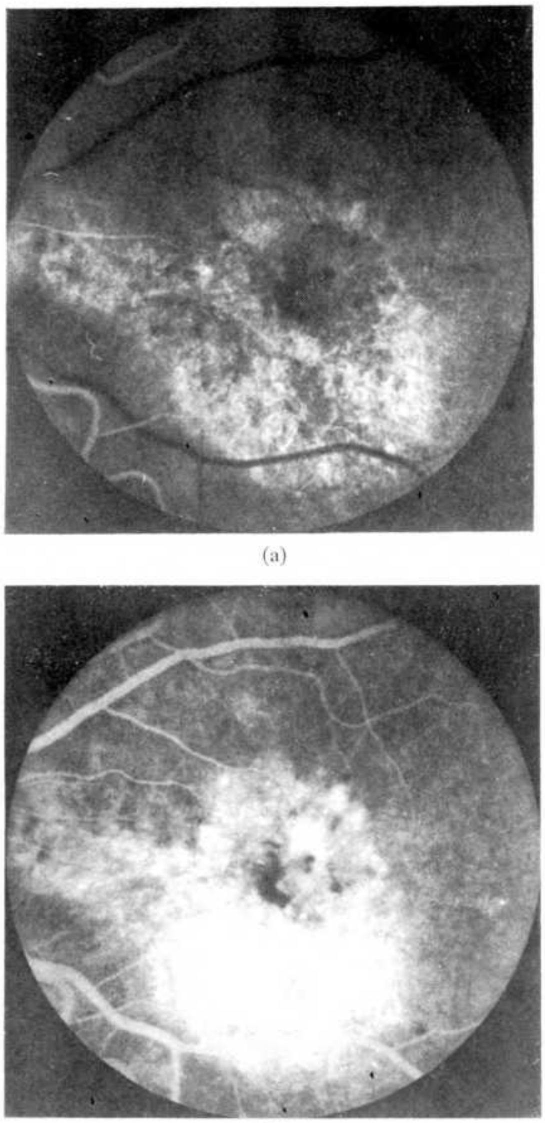


FIG. 1 *Case 1. Changes in appearance of left posterior polar lesion involving the macula.* (a) *On presentation.* (b) *After 15 months.* (c) *After 27 months.* (d) *After 40 months*

showed gross swelling of the optic disc and a small pigmented lesion on its temporal side (Fig. 4). The superficial disc capillaries appeared engorged and retinal folding could be seen between the pigmented mass and the disc. A papillitis or tumour involving the optic nerve head was tentatively diagnosed and the patient admitted to hospital for further investigations.

General physical and neurological examination was negative, as were the results of x-ray examination of skull and optic foramina, carotid angiograms, and air encephalograms. A full blood count and plasma viscosity estimation were within normal limits. A trial of systemic corticosteroids produced no improvement in symptoms. When seen in January 1974 the patient's visual status had not altered. The disc, however, appeared less swollen and the pigmented area temporal to the disc was more obvious and clearly defined. He had an eosinophilia of 8 per cent and a toxocaral fluorescent antibody test proved positive. The patient denied recent contact with dogs or puppies. Subsequent examinations at



(a)

(b)

FIG. 3 *Case* 1. *Left retinal fluorescein angiograms at 40 months.* (a) *Early arterial phase.* (b) *Residual angiogram. Extensive retinal pigmentary disturbances are now an obvious feature, with minimal uptake or leakage of dye in residual phase*

six-monthly intervals showed a gradual decrease in disc swelling and progressive pigmentation of the retina temporally.

Fluorescein angiography

Fluorography of the right retina in August 1973 showed dilatation of the prepapillary capillary plexus and masking of the choroid in the region of the pigmented lesion in the early phase of the transit. In the residual phase there was profuse leakage of dye from the disc capillaries and uptake of fluorescein in the centre of the pigmented lesion (Fig. 5*a*, *b*). Fluorescein studies in November 1975 showed that the dilated capillaries overlying the disc were less prominent than before, with reduced leakage of dye from these vessels. There were extensive pigmentary disturbances in the area around the retinal lesion described on presentation but no leak or uptake of dye was recorded.

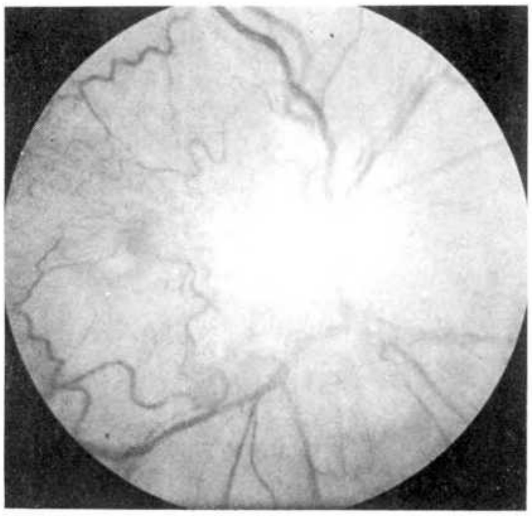
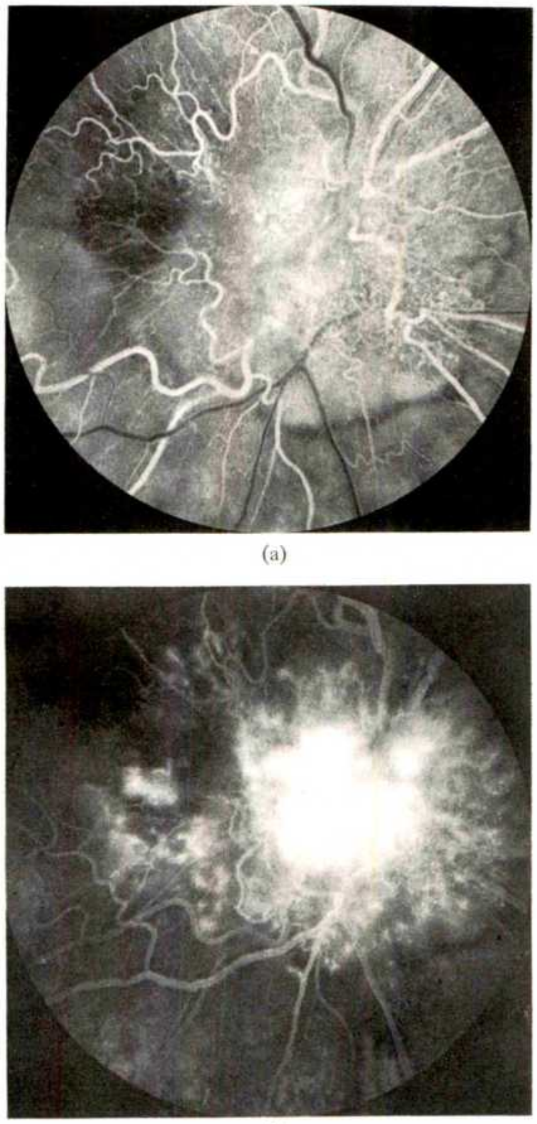


FIG. 4 *Case* 2. *View when patient presented of right swollen disc and mass at* 9 *o'clock*

CASE 3

A 20-year-old bank clerk was seen at the Bristol Eye Hospital in November 1974 with a history of gross impairment of left central vision of nine months' duration. Visual loss had been rapid. He had no other symptoms and his health had been good. He had initially attended another eye unit, where retinochoroiditis had been diagnosed. It was first thought that the retinal changes might be due to *Histoplasmosis capsulatum* infection, but a histoplasmin test was negative, as was a Mantoux test. A full blood count showed nothing abnormal. On examination in Bristol his right visual acuity was 6/6 and his left was hand movements. A large left central scotoma was plotted. No abnormalities were noted in the anterior segment or vitreous of his left eye, but ophthalmoscopy showed a raised pale area involving the macula, with surrounding pigment changes and some small retinal haemorrhages around the periphery of the lesion (Fig. 6). No abnormal features were found in the right eye. A toxocaral fluorescent antibody test was positive. The patient admitted frequent contact with a dog at his parents' home.

When seen in October 1974 his visual status remained unaltered but the changes at the posterior pole covered a wider area with obvious retinal pigmentary disturbances. Nine months later his visual acuity had not



(a)

(b)

FIG. 5 *Case 2. Retinal fluorescein angiograms on presentation.* (a) *Early venous phase.* (b) *Residual angiogram. Prepapillary capillary plexus dilated. Massive leakage of fluorescein dye from these vessels is prominent feature in residual angiogram*

improved. Although the mass appeared flatter than on presentation pigmentation of the retina continued to progress.

Fluorescein angiography

Retinal fluorography on his first visit to the Bristol Eye Hospital showed early masking of the choroidal fluorescence in the left eye and a later uptake of dye in the centre of the lesion as described in cases 1 and 2. Repeat angiograms in July 1975 showed merely a localized pigmentary disturbance without leak or uptake of dye.

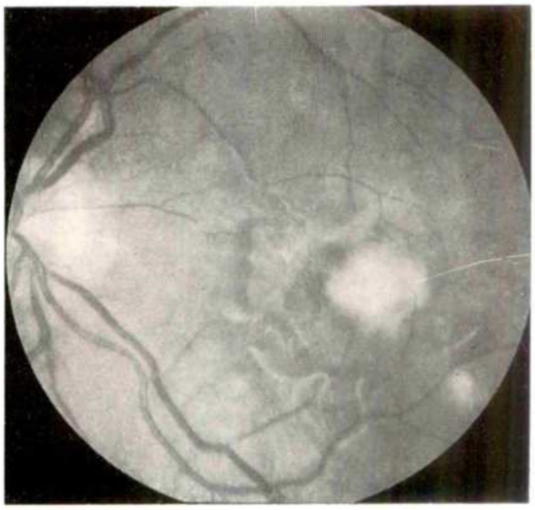


FIG. 6 *Case 3. Left eye on presentation. View of pale raised lesion involving macula*

Discussion

The ophthalmoscopic appearances of toxocaral retinal granulomata at the posterior pole were described in four children by Ashton (1960). He reported retinal lesions which were solitary, pale, discrete, circular, and raised. Blood vessels prominent on the edge of the mass became lost from view in the central area in two cases, and retinal haemorrhages adjacent to granulomata were reported in two further cases. The initial retinal findings in the adults reported in this series showed many of the features mentioned by Ashton. Moreover, we have followed the progressive nature of the retinal lesion in case 1 for $3\frac{1}{2}$ years from almost the initial to a late, less active stage. We believe that all three cases show manifestations, on presentation and later, which fit into a definite clinical pattern not previously described in adults.

On entering the systemic vascular circulation the second stage toxocaral larva is washed along in the blood stream until arrested in a vessel whose calibre permits no further progress. The organism, a very active borer (Sprent, 1954), then passes through the vessel wall and takes up a position deep in the tissues, where it may remain alive for a long time. We suggest that retinal haemorrhages produced by the passage of the larva through the vessel wall and sudden subsequent movements of a foreign organism adjacent to the macula could cause the initial retinal visual disturbances, and that as the parasite becomes less active retinal function may transiently improve, as in case 1.

Eventually, however, the larva dies and disintegrates, prompting an intensified tissue response which leads to focal disruption of the neural layers of the retina (Ashton, 1960) and disturbances of the pigment epithelium. During this active inflammatory stage increased vascularity in the region of the mass might be expected, and the local vascular dilatation in cases 1 and 2 suggests that a similar process could have happened in these patients. Later, as the cellular activity becomes reduced, flattening of the mass occurs, the vessels return to their previous calibre, and disturbances of the pigment epithelium promoted by the earlier inflammatory response appear more obvious and widespread.

The fluorescein studies in all cases showed initial masking of the choroidal phase at the site of the pigmented lesion due to thickening or opacification, or both, of the overlying retina, and the localized hyperfluorescence in the residual phase probably resulted from uptake of dye into cystic spaces or staining of inflammatory tissue. Later studies showed extensive pigmentary disturbances at the posterior pole with no leakage of fluorescein dye, corresponding to a less active phase of the disease process. In case 2 marked dilatation of the prepapillary capillary plexus was a prominent feature, and possibly the process was fairly active when the patient first presented. The initial ophthalmoscopy changes were similar to those in a case of nematode optic neuritis reported by Bird and others (1970).

Unilateral ocular pain or headache was a prominent symptom in two of our patients. Severe retro-ocular pain was completely relieved within 24 hours by vigorously light-coagulating the site presumed to be occupied by a larva in a patient who presented with evidence of toxocariasis (Raistrick and Dean Hart, 1975). Apparently the living organism may cause this symptom, since ocular pain was also relieved after thiabendazine treatment in a presumed case of ocular toxocaral infection (Unsworth and others 1965).

The soil of many recreational areas in and around towns and cities of the United Kingdom is heavily contaminated with the live ova of toxocara. Borg and Woodruff (1973) found ova of *Toxocara* species in 24·4 per cent of 800 soil samples taken from public places. As such open spaces are used for picnics and sporting activities there is ample opportunity for ova to enter the human body. Children of dog owners may no longer be assumed to be the only section of the community exposed to this hazard, nor can the absence of a history of contact with animals that might harbour the parasite exclude the diagnosis.

Although histological verification of toxocaral lesions involving the retinae of adults is lacking toxocara larvae were probably alone responsible for the lesions in our patients, and this diagnosis should be considered in adult patients presenting with similar symptoms and signs.

Summary

Human infection by toxocara larvae has been thought to be predominantly a disease of young children, but the percentage of the population with antibodies to this nematode worm has recently been shown to increase with age. Although a definite diagnosis of ocular toxocariasis can be made only by identifying the larva histologically, the evidence in three cases presenting with recent uniocular loss of vision strongly suggests that adults may also be affected. The lesions noted on ophthalmoscopy closely resembled toxocaral granulomata in children. Toxocaral fluorescent antibody tests were positive in each case.

We thank Professor A. W. Woodruff for advice and his staff for performing the toxocaral fluorescent antibody tests. We thank Mr J. Morgan for photographic services, and Mrs M. Roach for her secretarial help.

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Synapse formation in retinoblastoma tumours

D. HOWARD DICKSON,*[1] MICHAEL S. RAMSEY,†[2] AND JOHN G. TONUS*
From the Departments of Anatomy, Ophthalmology, and Pathology,†*
Dalhousie University, Halifax, Nova Scotia, Canada

Although several papers have recently been published on the ultrastructure of retinoblastoma tumours (Ts'o, Fine, and Zimmerman, 1969a, 1970; Ts'o, Fine, Zimmerman, and Vogel, 1969b; Choux, Tripier, Bérard, Hassoun, and Toga, 1972; Sevel, Röhm, and Sealy, 1974; Radnót, 1975) the discovery of synapse formation in this type of tumour pointed to new information on the histogenesis of retinoblasts.

Materials and methods

A portion of a retinoblastoma tumour which had been fixed in 10 per cent neutral buffered formalin was prepared for transmission electron microscopy. After postfixation in osmium tetroxide and dehydration in graded alcohols and propylene oxide the tissue was embedded in Durcupan, and sectioned and examined in a Philips 300 electron microscope.

Results

Previous light microscopical examination of the globe had confirmed the presence of a retinoblas-

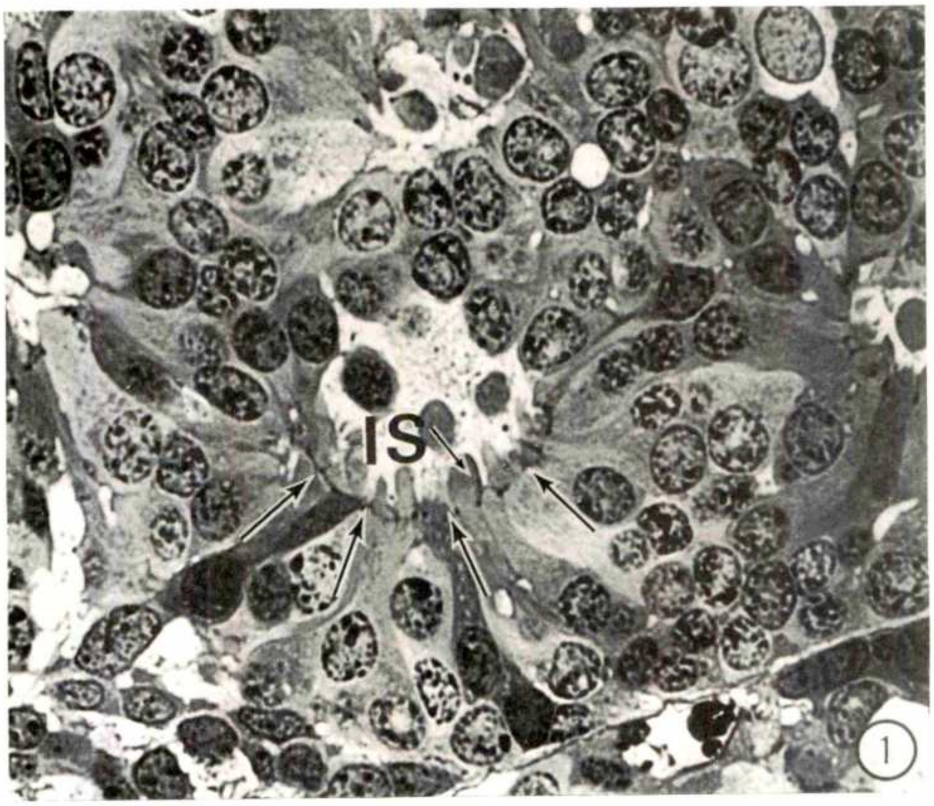

FIG. 1 *Light micrograph of 0·5 μm plastic section of retinoblastoma fleurette. Some cells show features of photoreceptor differentiation which include elongated inner segment regions (IS) that project beyond fenestrated membrane (arrows) into lumen of fleurette.* ×2000

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Address for reprints: Dr D. Howard Dickson, Department of Anatomy, Sir Charles Tupper Medical Building, Dalhousie University, Halifax, Nova Scotia, Canada, B3H 4H7

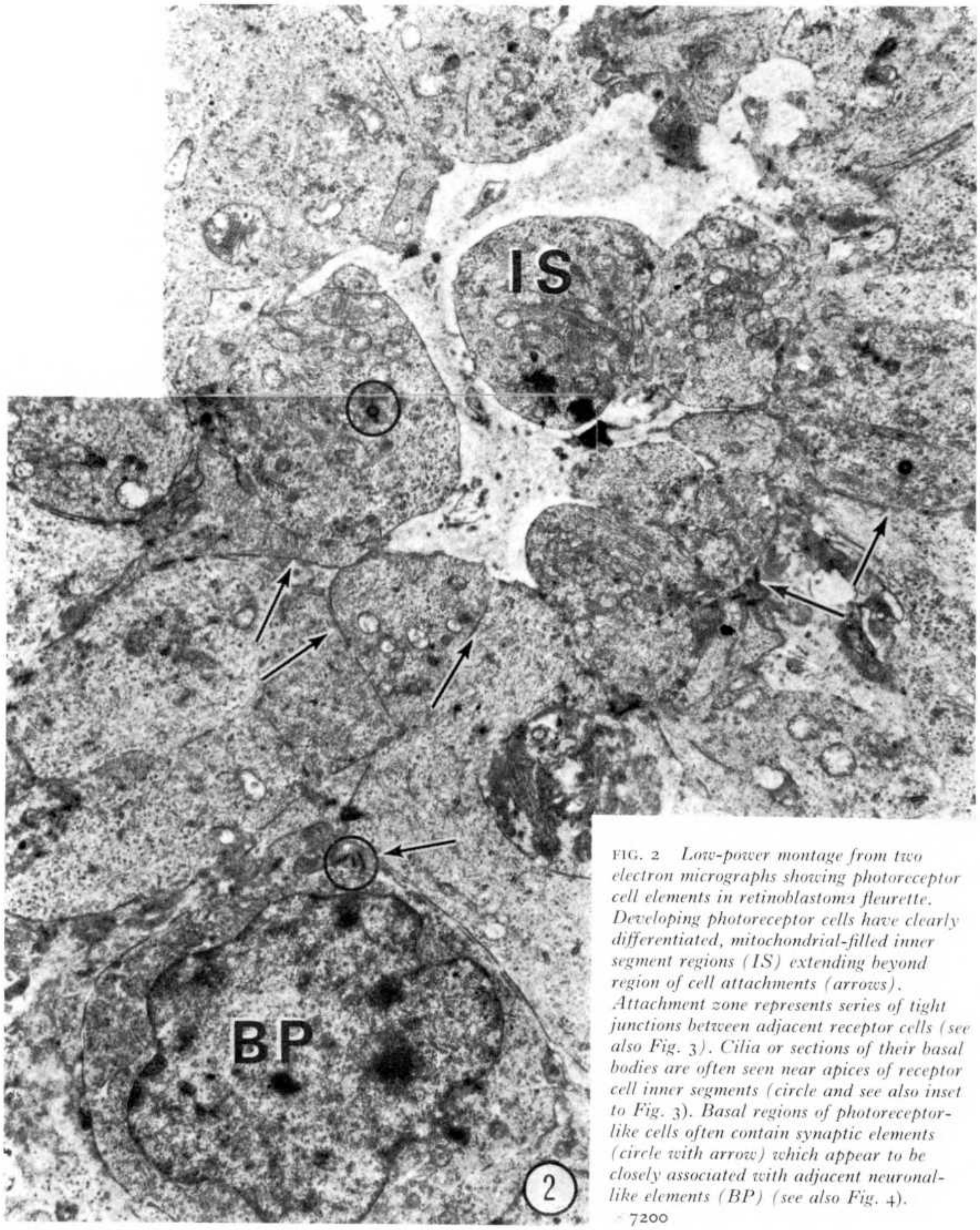

FIG. 2 *Low-power montage from two electron micrographs showing photoreceptor cell elements in retinoblastoma fleurette. Developing photoreceptor cells have clearly differentiated, mitochondrial-filled inner segment regions (IS) extending beyond region of cell attachments (arrows). Attachment zone represents series of tight junctions between adjacent receptor cells (see also Fig. 3). Cilia or sections of their basal bodies are often seen near apices of receptor cell inner segments (circle and see also inset to Fig. 3). Basal regions of photoreceptor-like cells often contain synaptic elements (circle with arrow) which appear to be closely associated with adjacent neuronal-like elements (BP) (see also Fig. 4).*
× 7200

toma with tumour-cell appearances ranging from undifferentiated neuroblastic cells to incomplete rosettes and to well-formed Flexner-Wintersteiner rosettes and fleurettes (Dickson, Ramsey, Tonus, and Goldberg, 1976).

The fleurettes were in the form of asymmetric tumour-cell clusters with some of the cells forming elongated photoreceptor-like elements (Figs 1 and 2). These cells had long apical cytoplasmic processes joined by a fenestrated membrane which the

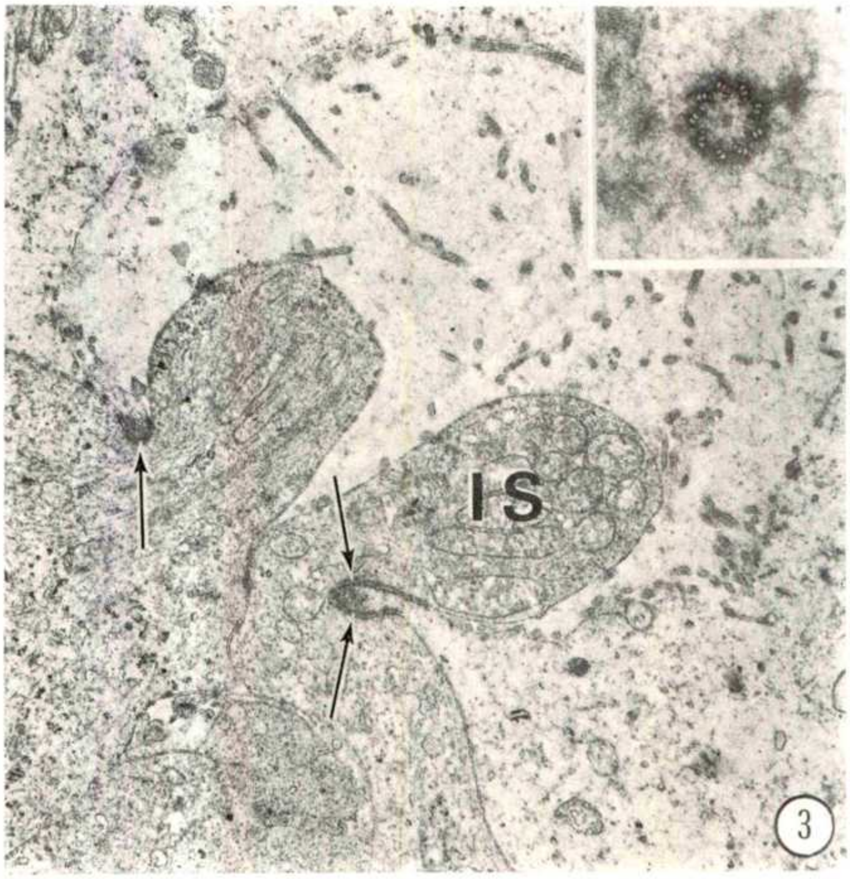

FIG. 3 *Electron micrograph of mitochondrial-filled inner segment regions of two developing photoreceptor elements from retinoblastoma fleurette. Mitochondria and microtubular structures seen within bulbous inner segment regions (IS) and apical tight-junctional complexes between adjacent cells (arrows).* Inset: *high resolution micrograph of basal body region of cilium in Fig.* 2. × 9500. Inset × 53 300

electron microscope showed to be composed of a series of tight junctions between adjacent receptor-like cells (Figs 2 and 3). The distal cytoplasmic processes of these developing receptor-like elements were expanded to form bulbous mitochondrial-filled endings. The apices of these cells contained a cilium and an abundance of microtubular structures typical of the inner segment regions of normal human photoreceptors. In addition, their basal regions contained synaptic elements which included elongated synaptic ribbons each with an arciform density and surrounded by clear synaptic vesicles measuring about 45 nm in diameter (Figs 2, 4, and 5). These terminals appeared to be making functional invaginated synapses with adjacent neuronal-like elements. The postsynaptic cells located near the basal regions of the receptor elements presented spherical profiles and were more electron dense than the presynaptic receptor elements.

The synaptic arrangements presented here are identical in appearance to the photoreceptor-bipolar cell synapses in the normal human retina.

Discussion

The electron microscopical appearance of retinoblastoma fleurettes was described first by Ts'o and others (1969b) and was reported to represent a much more advanced stage of tumour cell differentiation than the Flexner-Wintersteiner rosettes described by Ts'o and others (1969b). Our data would clearly substantiate the present evidence on the ultrastructural characteristics of photoreceptor-like elements in retinoblastoma fleurettes. These include apical tight-junctional complexes between adjacent cells; apical mitochondrial-filled expansions (presumably developing inner segment ellipsoids), and apically positioned cilia. In addition, we have found further evidence of the advanced state of differentiation of this tumour in the form of receptor-cell synapses with adjacent neuronal elements.

The synaptic elements reported here are composed of synaptic ribbons (lamellae) and arciform densities within the basal region of the developing receptor-like cells. These ribbons were found to be surrounded by clear, 45 nm vesicles. Further,

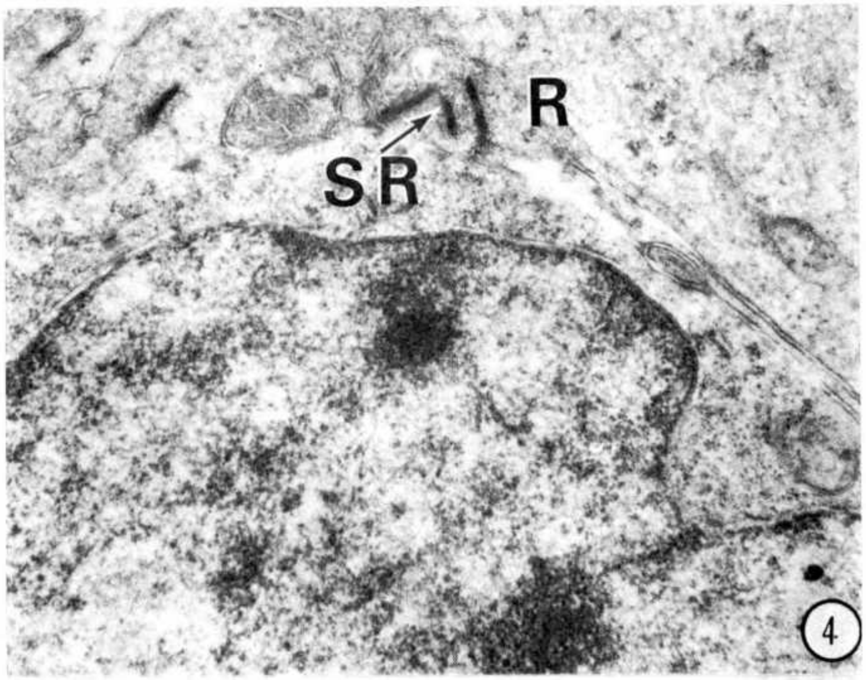

FIG. 4 *Electron micrograph of synaptic area indicated by circle with arrow in Fig. 2. Synaptic elements visible include synaptic ribbons (SR) and associated synaptic vesicles. R = receptor cell. BP (Fig. 2) = postsynaptic neuronal element.* ×28 500

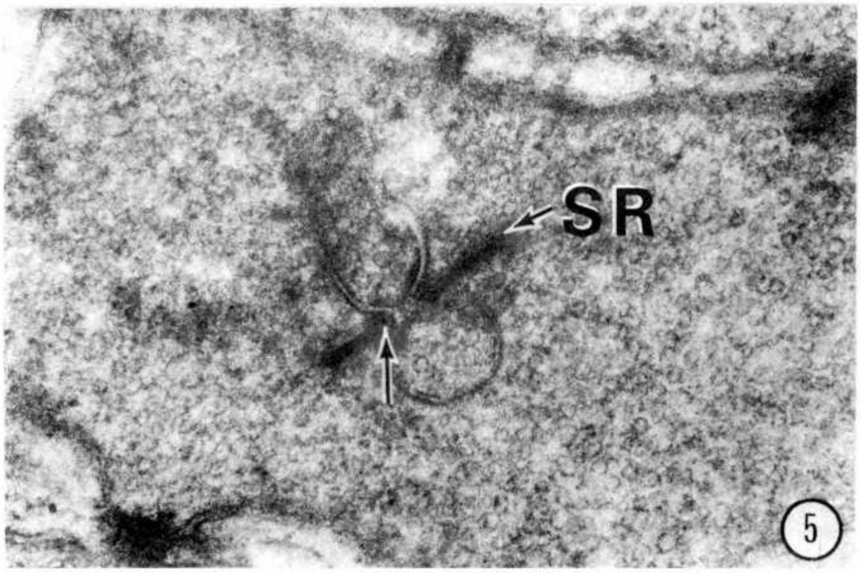

FIG. 5 *High resolution electron micrograph of receptor cell terminal (R) with two synaptic ribbons (SR), one with arciform density (arrow) and both surrounded by clear, 45-nm synaptic vesicles. Invaginated synapse occurring with adjacent neuronal element (BP (Fig. 2)).* ×57 300

these receptor-like cells made close invaginated contact with basally located cells, which we suggest represent tumour cell differentiation along the lines of bipolar neurons. This whole complex appears in all respects to be analogous to the outer plexiform layer synaptic associations between normal human photoreceptor cells and bipolar neurons.

Synaptic vesicles were first reported in retinoblastoma Flexner-Wintersteiner rosettes by Choux and others (1972), but they did not identify synaptic ribbons associated with the vesicles. Radnót (1975) has identified isolated examples of synaptic lamellae in retinoblastoma tumour cells. She has not, however, reported these structures within developing receptor cells.

According to Spira and Hollenberg (1973) functional synapses are seen in developing human retinas before the formation of outer segment disc membranes. The presence of a synaptic apparatus but absence of outer segment discs from the developing receptor cells in the fleurettes of this tumour suggests further proof of a similarity in development between normal human retinal receptors and the receptor-like cells of retinoblastoma tumours.

Further, our study would suggest that retinoblastoma rosettes and fleurettes represent sequential or progressive stages of tumour differentiation along photoreceptor lines. From the work of Choux and others (1972) and our findings (Dickson and others, 1976) initial synapse formation appears to begin at the rosette stage with a bulbous vesicle-filled sac near the base of the developing receptor cell. Later, in the fleurette stage, a synaptic ribbon forms and invaginated postsynaptic contact is established with other developing neuronal elements to form a functional synapse.

Summary

Developing photoreceptor-like cells in retinoblastoma tumour fleurettes were found to contain apical tight junctions, mitochondrial-filled inner segment regions with cilia, and basally located synaptic ribbons and vesicles. Synaptic contact appeared to be established with adjacent neuronal-like elements. We suggest that photoreceptor differentiation in retinoblastoma tumours follows a sequence similar to normal human photoreceptor embryogenesis.

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Cryoprobe with T-tip for retinal surgery

M. G. LYALL
From the Regional Eye Centre, Oldchurch Hospital, Romford, Essex

A cryoprobe with a T-tip designed to facilitate cryotherapy in retinal surgery is described in this paper.

The T-tip cryoprobe (Figs 1 and 2) is modelled on the thimble indentor of Schepens (1950). In my experience the conventional cryoprobe when used as an indentor in monitored cryopexy operations may show up retinal holes and tears less well than the thimble indentor. Also it may be difficult to manoeuvre the conventional probe, so that a large tear is completely surrounded by treated areas. Furthermore, as Chignell, Revie, and Clemett (1971) indicate, when there is a large area to be treated refreezing may be carried out inadvertently with danger of pigment fall-out and macular damage. Lastly, when a large area has to be treated—for example, in peripheral retinal dialysis—it takes a long time to give the large number of applications necessary. The T-tip probe treats a larger area with each application and so reduces the number of applications needed. Time-saving techniques are advantageous, since operative concentration and skill tend to fall off after two hours.

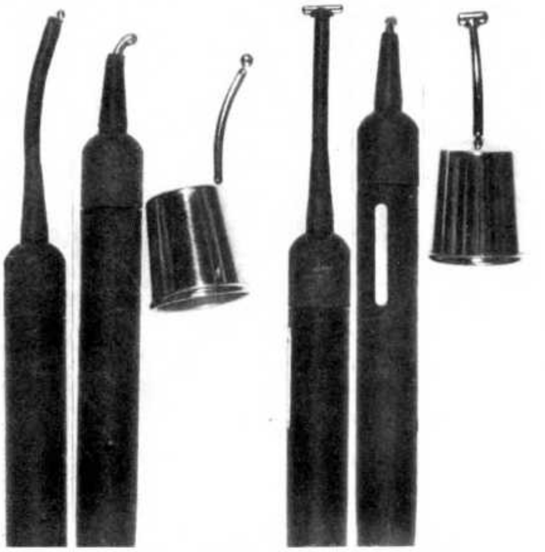

FIG. 1 and FIG. 2 *T-tip cryoprobe, conventional cryoprobe, and thimble indentor*

Method of use

Obviously, the T-probe indents as the thimble indentor. Most tears are dealt with readily by three applications. The first is given so that the freeze reaches the posterior rounded margin of the tear, the second is given across the tear, and the third touching the anterior angles of the tear (Fig. 3). After the first application it is a simple matter to bring the probe forwards for the next freeze and then the third. Areas of lattice or lattice with holes are readily treated, since they are usually disposed in a circumferential fashion and one or two applications in any meridian are usually enough. Similarly, dialyses can be conveniently treated.

Monitoring shows that the freeze appears first in one area of the indent and then spreads to the remainder. As with the conventional probe, the freeze is delayed in transconjunctival cryotherapy when an area of choroid deep to a muscle is being treated. Satisfactory pigmentation of Chignell's Grade II type (Chignell and others, 1971) is produced with appropriate application. I have used the probe in over 20 cases, producing with it a pigment macular fall-out in one case in which there were three large horseshoe tears and macular detachment.

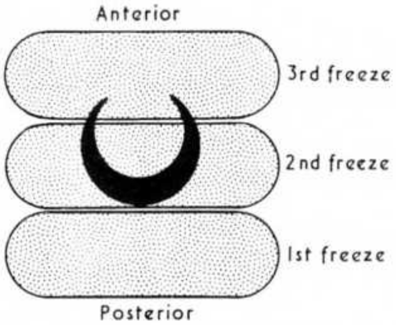

FIG. 3 *Freeze pattern in treatment of common horseshoe tear*

The T-tip cryoprobe attaches to Amoils cryo unit. It is available from Keelers, London. A similar model for use with the MC1000 cryosurgical system is available from KeyMed, Southend-on-Sea.

Address for reprints: M. G. Lyall, FRCS, Oldchurch Hospital, Regional Eye Centre, Romford, Essex

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Indocyanine green fluorescence angiography of the choroid

A. CRAANDIJK AND C. A. VAN BEEK
From the Eye Hospital, The Hague, The Netherlands

The introduction of fluorescence angiography by Novotny and Alvis (1960) was an important advance in our knowledge of the circulation and pathology of the retina. Our knowledge of the choroidal circulation is limited to cases of disease of the pigment epithelium and the choriocapillaris. Not only is visible light unable to penetrate the pigment epithelium and macular pigment but also fluorescein in the choriocapillaris rapidly leaks, obliterating vessel detail. The peculiar anastomosing of the vessels of the choroid parallel to the optic axis also contributes to the relative invisibility of the choroid.

Kogure, David, Yamanouchi, and Choromokos (1970) first demonstrated choroidal angiography in the Owl monkey using indocyanine green (ICG) with the 'false colour' infrared aero film. Drawbacks to this method are the high concentration of indocyanine green needed, the arterial injections, and the inconsistency of the false colour film. Hochheimer (1971) used black and white infrared film, and injected the indocyanine green intravenously in the cat. Flower (1972) showed that intravenous ICG absorption angiography could be performed repeatedly in man. Infrared light absorbed by ICG shows the filling of the large choroidal and retinal vessels but little filling of the arteries and capillaries.

Flower and Hochheimer (1973) described a method of ICG fluorescence angiography in which the arterial and capillary dye phases could be seen. A year later Flower (1974) developed a camera which simultaneously records fluorescein, ICG absorption, and ICG fluorescence angiography. An extensive modification of the Zeiss fundus camera with two beam splitters, an intermediate relay lens, and three Nikon cameras was used in such a manner that the passage of the dye fronts could be recorded simultaneously on the three different films. From this it became apparent that the larger retinal and choroidal vessels are seen best on ICG absorption angiographies, whereas the smaller choroidal vessels are seen best on ICG fluorescence angiograms.

Our study was designed to reproduce Flower's results and to assess the potential clinical usefulness of ICG fluorescence angiography. Since we intended to record only fluorescence angiograms we were able to avoid the expense of extensive modifications of our camera.

Method

A Zeiss fundus camera was fitted with an exciter filter (interference filter with a peak at 777·5 nm) in the diaphragm disc in front of the flash tube (Fig. 1). The barrier filter (interference filter with a peak at 854·9 nm) fitted in a Zeiss 30° conus in front of the film in such a manner that the camera body was attached over the conus. The film (Kodak high speed infrared sensitive black and white film, HIE-135-20) was developed in Kodak D-19 developer at 20°C. The Beam flash unit was set at 600 W/s. Indocyanine green 25 mg was diluted with aqueous solvent so that 2 ml of ICG could be injected. The camera was firing at the rate of 1 frame/0·7 s and was started 8 seconds after the intravenous injection. The passage of the dye front could not be seen and there were only 20 frames available on the film.

Results

Several sets of ICG angiograms were compared with fluorescein angiograms which had been

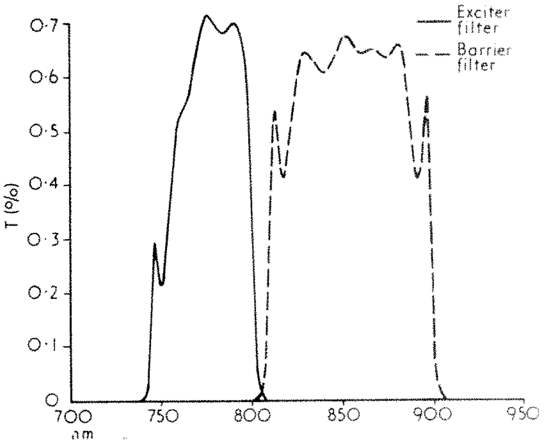
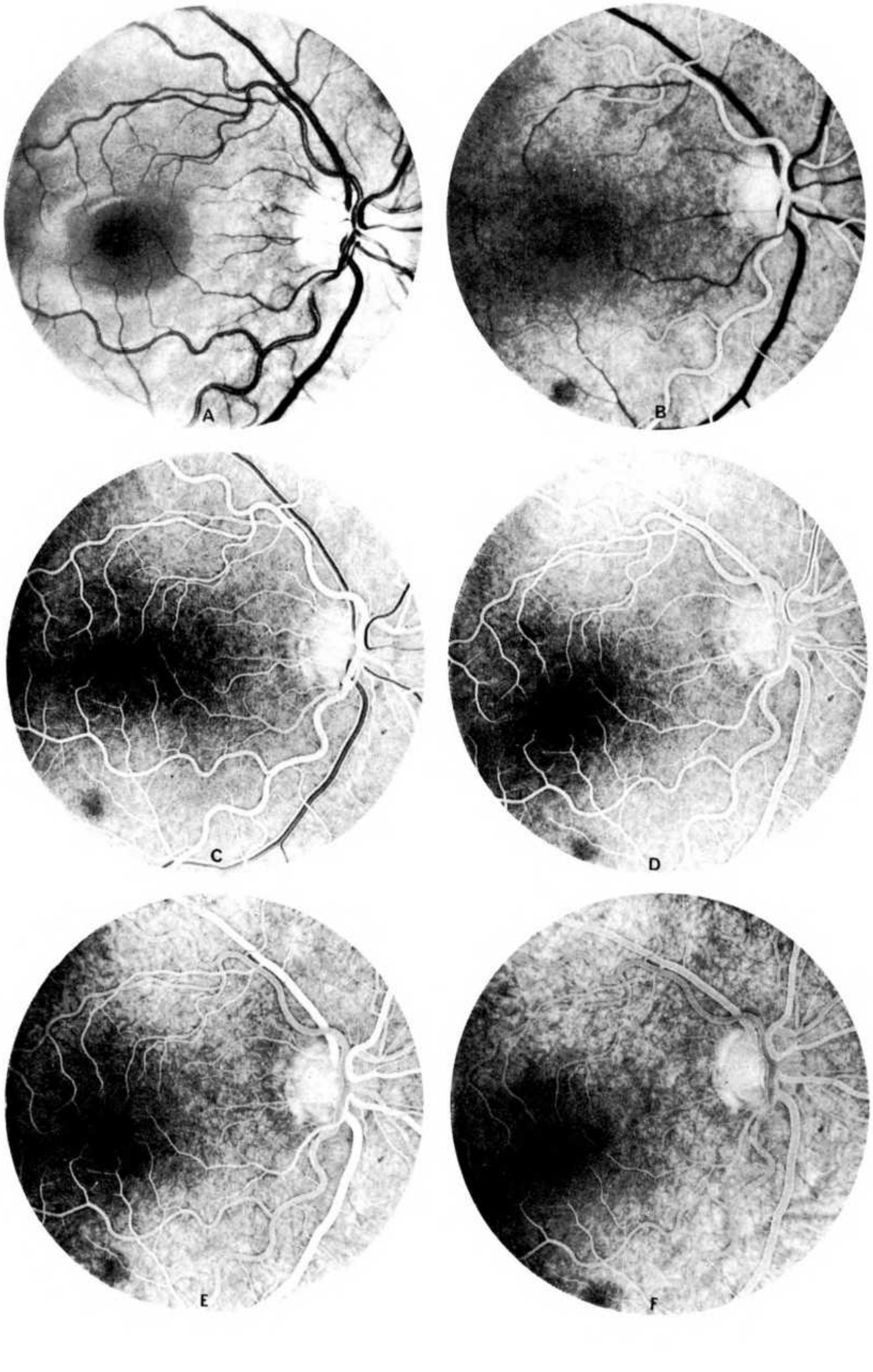


FIG. 1 *Transmission curve of the ICG exciter and barrier filters*

Address for reprints: A. Craandijk, MD, Eye Hospital, Leyweg 295, The Hague, The Netherlands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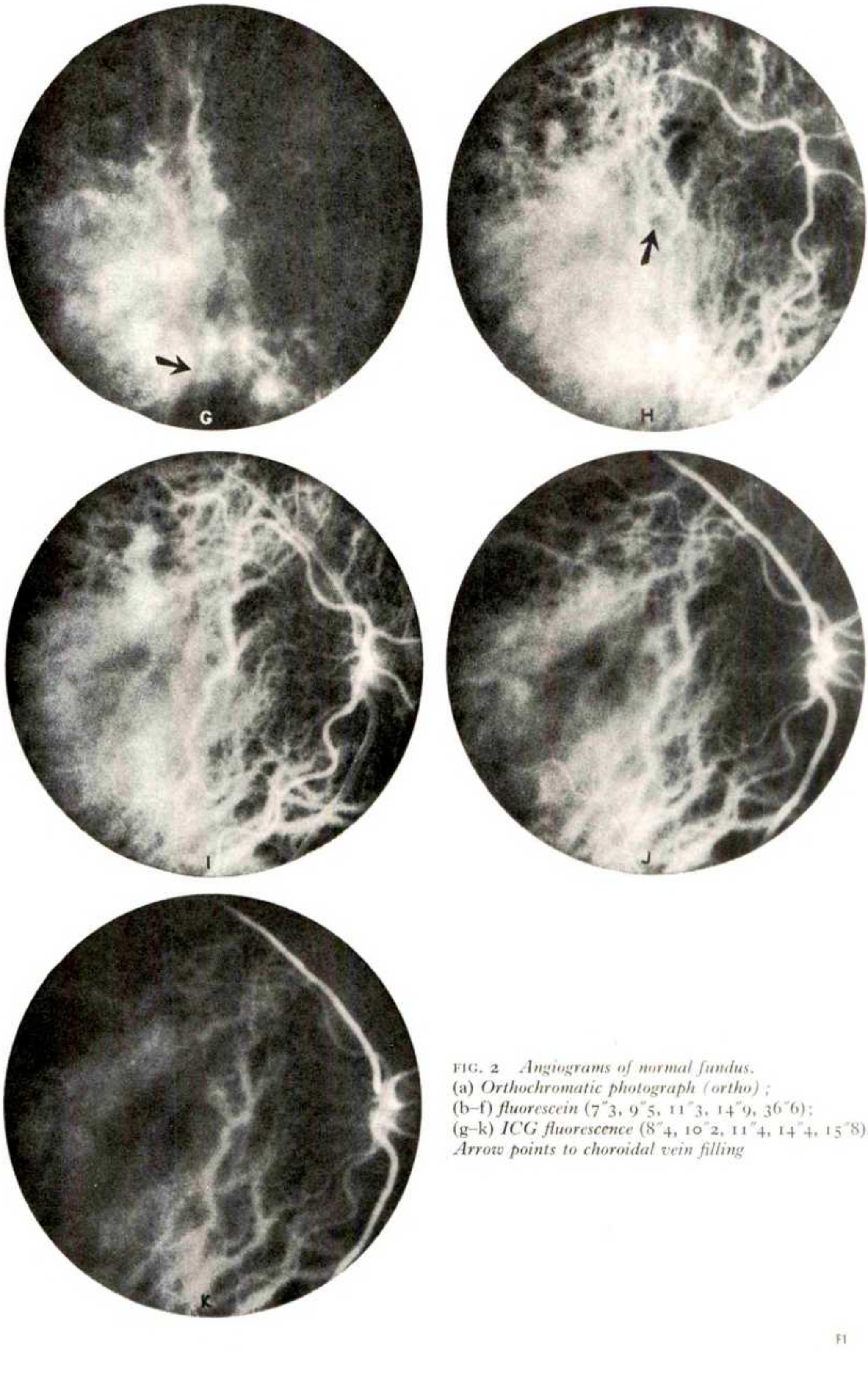


FIG. 2 *Angiograms of normal fundus.*
(a) *Orthochromatic photograph (ortho)*;
(b–f) *fluorescein* (7″3, 9″5, 11″3, 14″9, 36″6);
(g–k) *ICG fluorescence* (8″4, 10″2, 11″4, 14″4, 15″8).
Arrow points to choroidal vein filling

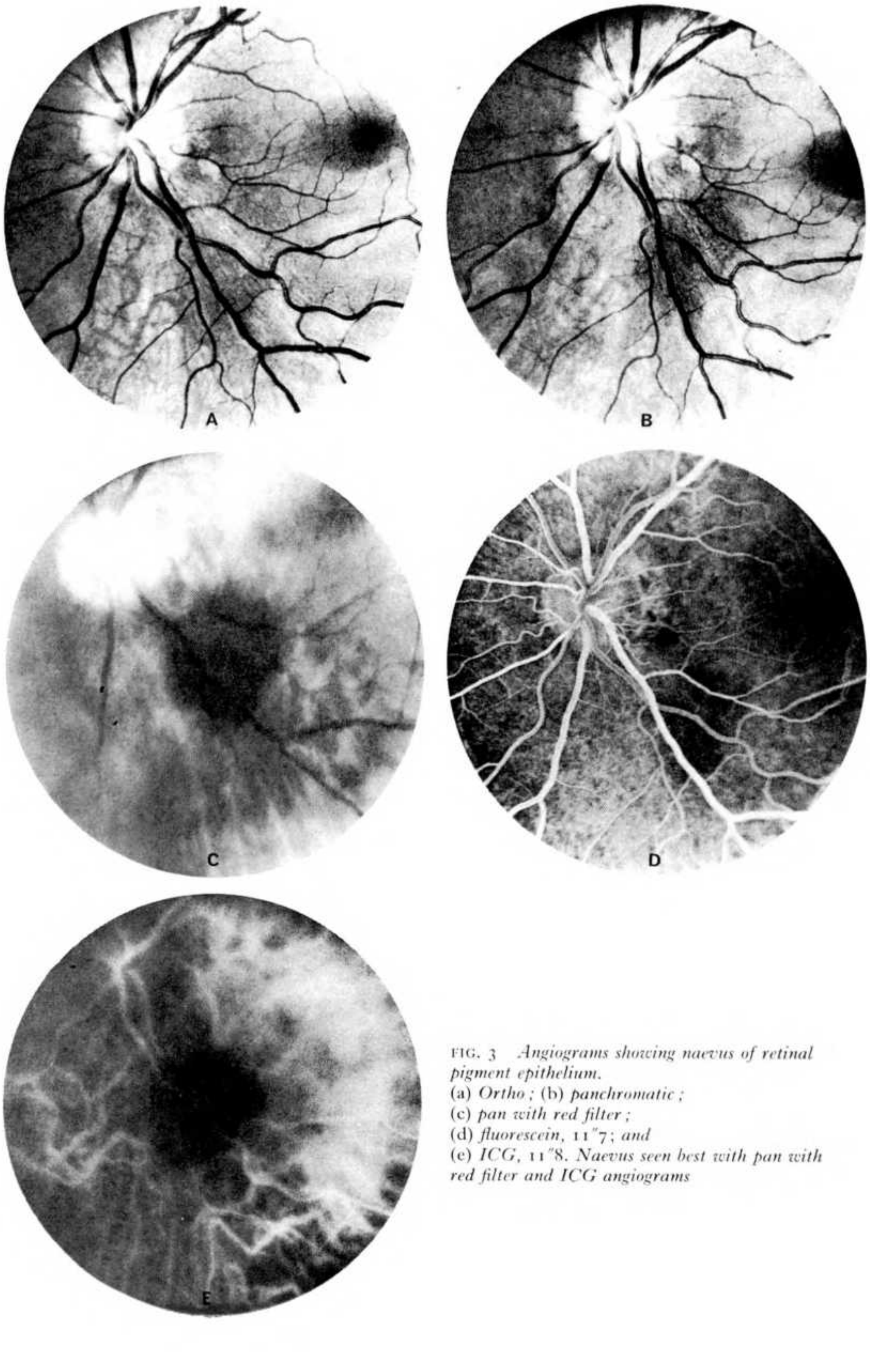


FIG. 3 *Angiograms showing naevus of retinal pigment epithelium.*
(a) *Ortho*; (b) *panchromatic*;
(c) *pan with red filter*;
(d) *fluorescein*, 11″7; *and*
(e) *ICG*, 11″8. *Naevus seen best with pan with red filter and ICG angiograms*

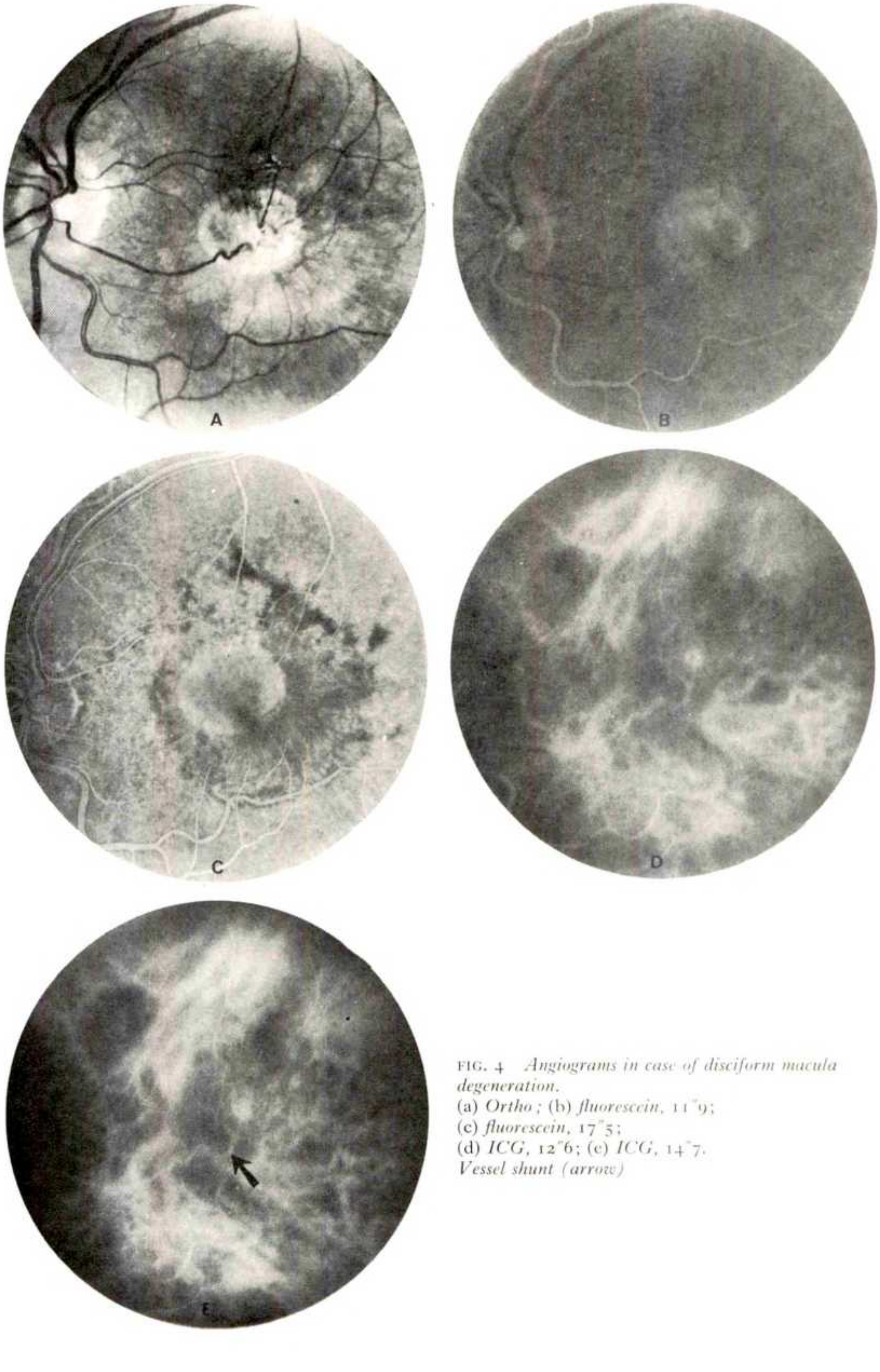


FIG. 4 *Angiograms in case of disciform macula degeneration.*
(a) *Ortho*; (b) *fluorescein*, 11″9;
(c) *fluorescein*, 17″5;
(d) *ICG*, 12″6; (e) *ICG*, 14″7.
Vessel shunt (arrow)

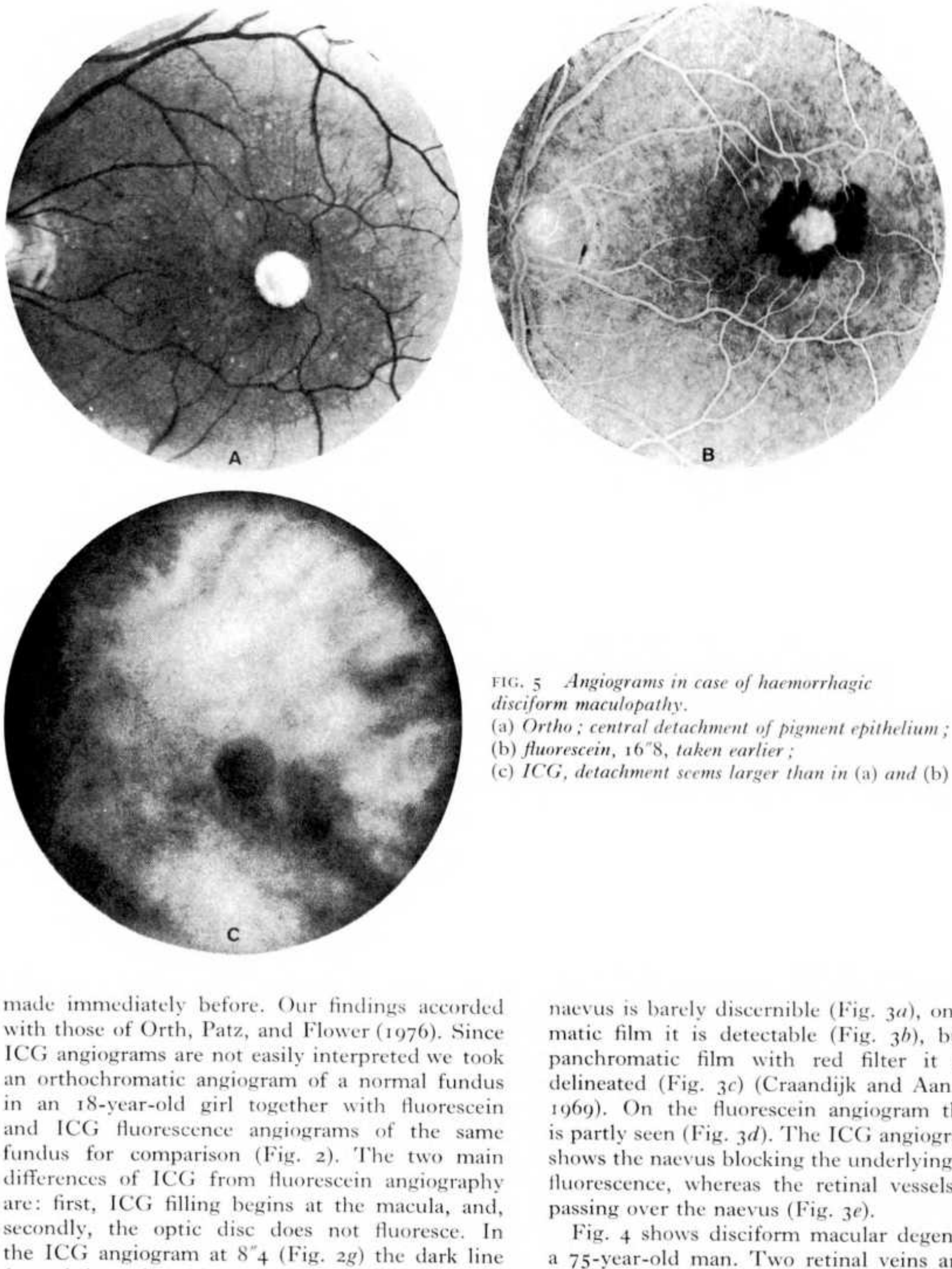


FIG. 5 *Angiograms in case of haemorrhagic disciform maculopathy.*
(a) *Ortho; central detachment of pigment epithelium;*
(b) *fluorescein, 16″8, taken earlier;*
(c) *ICG, detachment seems larger than in* (a) *and* (b)

made immediately before. Our findings accorded with those of Orth, Patz, and Flower (1976). Since ICG angiograms are not easily interpreted we took an orthochromatic angiogram of a normal fundus in an 18-year-old girl together with fluorescein and ICG fluorescence angiograms of the same fundus for comparison (Fig. 2). The two main differences of ICG from fluorescein angiography are: first, ICG filling begins at the macula, and, secondly, the optic disc does not fluoresce. In the ICG angiogram at 8″4 (Fig. 2*g*) the dark line (arrow) is a choroidal vein with maximum filling at 14″4 (Fig. 2*j*). The central dark spot persists throughout the series and corresponds with a pigmented spot in the fluorescein angiograms at 14″9 (Fig. 2*e*).

Fig. 3 shows a naevus of the pigment epithelium in a 20-year-old man. On orthochromatic film the naevus is barely discernible (Fig. 3*a*), on panchromatic film it is detectable (Fig. 3*b*), but on the panchromatic film with red filter it is clearly delineated (Fig. 3*c*) (Craandijk and Aan de Kerk, 1969). On the fluorescein angiogram the naevus is partly seen (Fig. 3*d*). The ICG angiogram clearly shows the naevus blocking the underlying choroidal fluorescence, whereas the retinal vessels are seen passing over the naevus (Fig. 3*e*).

Fig. 4 shows disciform macular degeneration in a 75-year-old man. Two retinal veins are seen to disappear in the centre of the disciform lesion. In the fluorescein angiograms these veins can no longer be traced to the centre owing to the fluorescence of the disciform lesion itself (Fig. 4*b*, *c*). Also note the pigmentations above the disciform lesion. In the ICG angiograms the retinal veins seem to form a shunt with a choroidal vessel

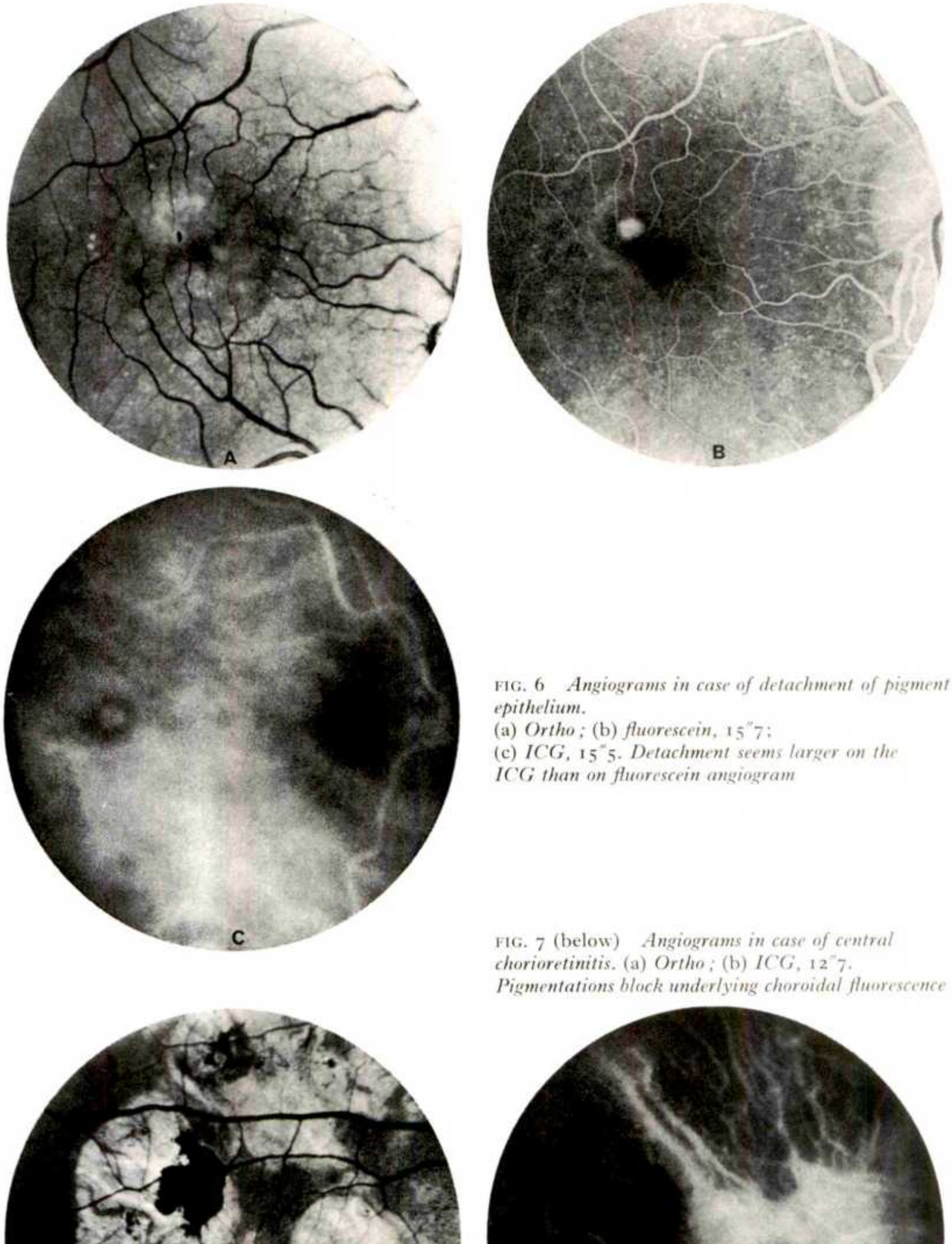
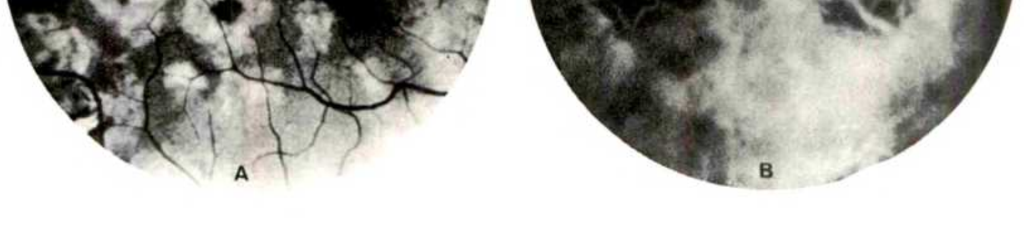


FIG. 6 *Angiograms in case of detachment of pigment epithelium.*
(a) *Ortho*; (b) *fluorescein*, 15″7;
(c) *ICG*, 15″5. *Detachment seems larger on the ICG than on fluorescein angiogram*

FIG. 7 (below) *Angiograms in case of central chorioretinitis.* (a) *Ortho*; (b) *ICG*, 12″7. *Pigmentations block underlying choroidal fluorescence*



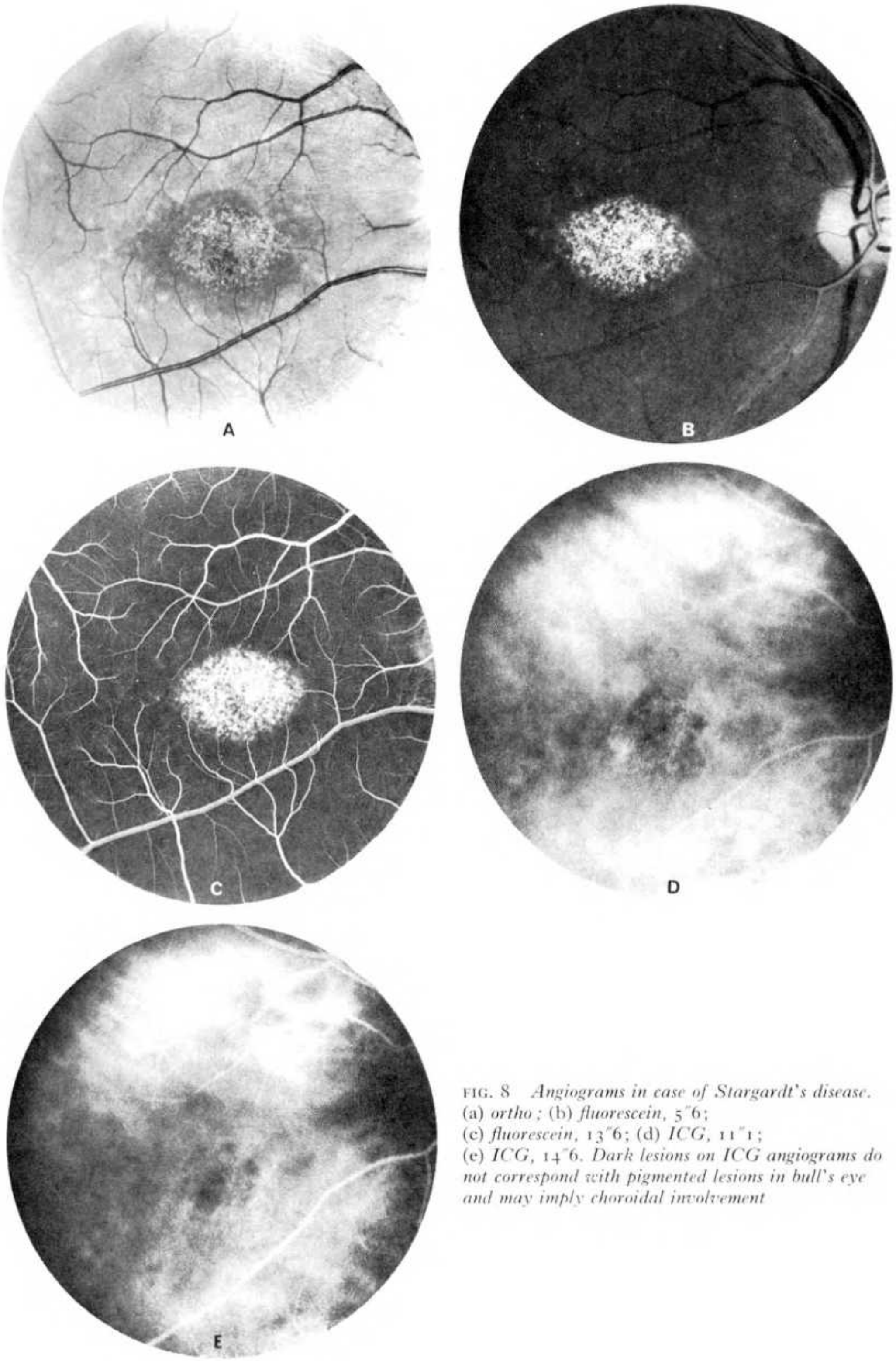


FIG. 8 *Angiograms in case of Stargardt's disease.* (a) *ortho*; (b) *fluorescein*, 5"6; (c) *fluorescein*, 13"6; (d) *ICG*, 11"1; (e) *ICG*, 14"6. *Dark lesions on ICG angiograms do not correspond with pigmented lesions in bull's eye and may imply choroidal involvement*

(Fig. 4*d*, *e* (arrow)). The pigmentations that were so clear in the fluorescein angiograms can be traced only with great difficulty in the ICG angiograms.

Fig. 5 shows a haemorrhagic disciform maculopathy in a 32-year-old man. The orthochromatic photograph shows the detachment of the pigment epithelium (Fig. 5*a*). Unfortunately the fluorescein angiogram taken a month earlier shows the detachment of the pigment epithelium with a collarette of haemorrhages (Fig. 5*b*). The ICG angiogram (Fig. 5*c*) shows the lesion to be larger than on the orthochromatic or on the earlier angiogram. These lesions correspond with those seen in cases of presumed ocular histoplasmosis.

Fig. 6 shows a detachment of the pigment epithelium in a 68-year-old man. The fluorescein angiogram clearly shows the detachment of the RPE (Fig. 6*b*), and on the ICG angiogram (Fig. 6*c*) this detachment seems to be larger.

Fig. 7 shows central chorioretinitis in a 60-year-old woman. The ortho angiogram shows a large pigmented lesion with choroidal vessels in the central atrophic area (Fig. 7*a*). On the ICG angiogram a much larger part than is to be expected is devoid of choriocapillaries (Fig. 7*b*). The pigmentations block the underlying fluorescence, whereas the larger choroidal vessels are seen in nearly all the atrophic areas.

Fig. 8 shows a case of Stargardt's disease in a 23-year-old man. The ortho angiogram shows the beaten bronze atrophy with the bull's eye in the centre (Fig. 8*a*). The fluorescein angiograms clearly show the bull's eye aspect (Fig. 8*b*). The ICG angiograms show pigment lesions in the centre (Fig. 8*c*). These cannot be proliferated pigment epithelium since they would have blocked the fluorescence in the fluorescein angiogram. Though rare, the choriocapillaris or the choroid may be involved (Deutman, 1971).

Discussion

The difference between the fluorescein and the ICG angiograms is obvious from these cases. Fluorescein angiography gives a better resolution and a better filling of the retinal vasculature. The choroidal vasculature is best demonstrated on ICG fluorescence angiograms, and is not limited to cases of diseased pigment epithelium and choriocapillaris. Orth, Patz, and Flower (1976) found differential leakage of fluorescein and ICG dyes in certain cases of neovascularization. We have limited ourselves primarily to macular lesions which could show differences in the fluorescein and ICG angiograms. Interpreting ICG angiograms takes far longer than fluorescein angiograms, partly because relatively little is known about the normal choroidal circulation.

ICG angiography does not require a very expensive adaptation of the camera, it can be performed in a few minutes, and can be followed by fluorescein angiography by changing the camera body and the syringe. We certainly agree with Flower that many more patients will need to be studied by different investigators before the clinical usefulness of ICG fluorescence angiography is proved.

Summary

Indocyanine green fluorescence (ICG) angiography of the choroid gives better visualization of the choroidal vessels than does fluorescein angiography. We found that the detachment of the pigment epithelium seems bigger on ICG than on fluorescein angiograms, and pigmented lesions are more clearly delineated.

The exciter and barrier interference filters were supplied by Ditric Optics, 247R Maple Street, Marlboro, Massachussetts 01752, USA.

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Multilobed uveal melanoma masquerading as postoperative choroidal detachment*

JERRY A. SHIELDS, BRIAN C. LEONARD, AND LOV K. SARIN
From the Oncology Unit, Retina Service, Wills Eye Hospital and Research Institute, Philadelphia, USA

It is well known that a choroidal detachment after intraocular surgery may clinically simulate a malignant melanoma of the uveal tract, and that such eyes have occasionally been enucleated with an erroneous diagnosis of malignant melanoma (Ferry, 1964; Shields and Zimmerman, 1973). The reverse situation, in which a malignant melanoma simulates a postoperative choroidal detachment, however, is extremely rare.

Case report

A 71-year-old myopic White woman was admitted to a local hospital because of dense cataracts in both eyes. Except for the lens opacities, which precluded a view of the fundi, her physical and ocular findings were reported to have been within normal limits. The patient underwent an uncomplicated cataract extraction in the left eye, followed one week later by a similar procedure in the right eye. At that time the left eye was noted to have a 'kissing choroidal detachment'. A retinal specialist agreed with the diagnosis and followed-up the patient conservatively for six weeks. Since the lesion failed to resolve the patient was referred to us for further evaluation to exclude the possibility of an intraocular tumour.

On examination the physical findings were normal except for mild hypertensive cardiovascular disease compatible with the patient's age. The positive findings were confined to the eyes. In the right eye the visual acuity was 6/24 with pinhole. There was surgical aphakia with a sector surgical coloboma superiorly. Ophthalmoscopy showed moderately advanced myopic chorioretinopathy with a clear vitreous. In the left eye the visual acuity was perception of light without projection and the intraocular pressure was 10 mmHg by applanation compared with 19 mmHg in the right eye. There was no evidence of excessive episcleral pigmentation. Through the left pupil a trilobed dark-brown mass was seen with the domes of the three lobes almost touching one another centrally. The inferotemporal lobe was displacing the ciliary processes centrally and the iris forward in that quadrant. Transillumination with a high-intensity fibre optics transilluminator showed no transmission of light through any of the lobes. B-scan ultrasonography showed a multilobed solid intraocular mass with a smooth surface and numerous internal reflections suggestive of either a tumour or haemorrhagic retinal detachment. Intravenous fluorescein angiography showed extensive leakage into the vitreous from the areas of detachment.

No definite diagnosis could be made. From the initial clinical studies the diagnosis was 'haemorrhagic choroidal detachment, rule out atypical malignant melanoma'. A transconjunctival (non-incisional) ^{32}P test was performed, comparing the inferotemporal mass with the symmetrical quadrant of the opposite eye. The procedure was performed with both the Detector Ocular Tumor Unit (EON Corporation) and the solid state semiconductor (Nuclear Associates, Technical Associates). The calculated percentage uptake was as follows:

Post injection	*EON unit*	*Solid state unit*
1 hour	143	145
24 hours	176	179
48 hours	205	230

This is considered a positive test (Hagler, Jarrett, and Humphrey, 1970; Ruiz, 1972; Shields, Sarin, Federman, Mensheha-Manhart, and Carmichael, 1974; Shields, Hagler, Federman, Jarrett, and Carmichael, 1975a).

Because the lesion so closely resembled a choroidal detachment rather than a melanoma we thought that the ^{32}P results might represent a 'false positive'. We therefore did an incisional ^{32}P test immediately after the 48-hour transconjunctival test. This assured closer approximation of the probe to the lesion. Because it gave a positive result by the transconjunctival technique the dense inferotemporal mass was tested, the superonasal lobe in the same eye being used as a control area. The percentage uptakes of the lesion over the control were as follows:

EON unit	*Solid state unit*
561	448

This was interpreted as an unequivocally positive test. Certain investigators have stated that a choroidal or subretinal haemorrhage can give a false-positive result

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Address for reprints: Jerry. A. Shields, Oncology Unit, Retina Service, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pennsylvania 19130

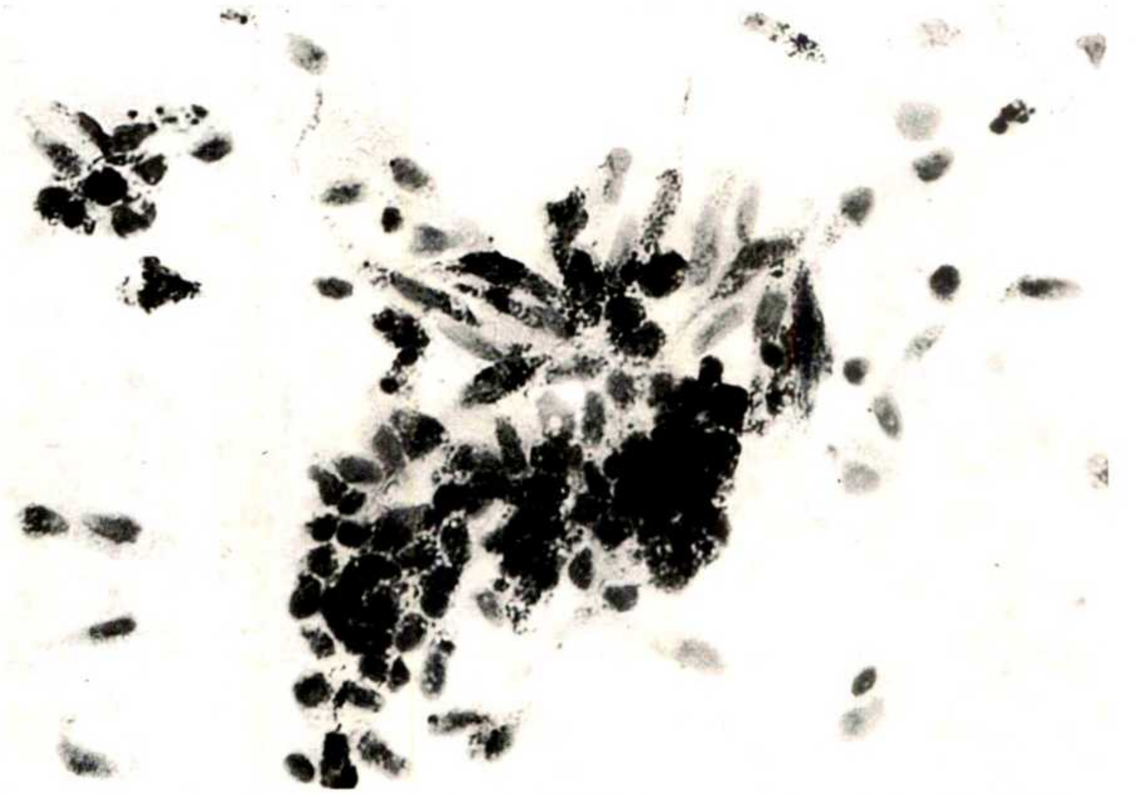

FIG. 1 *Biopsy specimen showing spindle-shaped cells with pigment. Diagnosis: malignant melanoma, spindle-B cell type. Haematoxylin and eosin.* × 640

to the ^{32}P test. We therefore obtained tissue for biopsy from the inferotemporal mass through a trap-door pars plana incision. Several pieces of loose pigmented material were carefully removed and the wound was securely closed. Histological examination within 15 minutes showed numerous spindle-B malignant melanoma cells (Fig. 1). The eye was subsequently enucleated.

Pathology

The globe measured 26 × 26 × 25 mm with 2 mm of optic nerve attached. There was a total retinal detachment with extensive haemorrhage and exudate in the subretinal space on the nasal side. On the temporal side the choroid was replaced by a large, multinodular pigmented tumour which filled almost one-half of the globe (Fig. 2).

Histologically the tumour consisted of predominantly spindle-B cells with occasional epithelioid cells (Callander classification). The biopsy site inferotemporally showed acute and chronic inflammatory cells superficially, but the tumour cells were confined within the globe. There was no evidence of extrascleral extension. Superiorly and nasally there was a total haemorrhagic and serous retinal detachment, which produced the dark elevations seen with the slit lamp.

Discussion

When a dark, multilobed mass is seen through the pupil of an eye with low intraocular pressure after cataract surgery the most likely diagnosis is a choroidal detachment. A serous choroidal detachment permits transillumination, whereas a dense haemorrhagic choroidal detachment, like a malignant melanoma, usually does not. This case had several features which were more suggestive of a haemorrhagic choroidal detachment than of a malignant melanoma.

A melanoma of the choroid or ciliary body is usually a solitary mass often associated with a serous detachment of the sensory retina. It is unusual for a melanoma to have a multilobed configuration or to produce an extensive haemorrhagic retinal detachment, as in this case. The haemorrhagic retinal detachment in the superior and nasal portions of the fundus produced dark, bullous masses which appeared identical clinically to the malignant melanoma in the inferotemporal fundus. Choroidal detachments after intraocular surgery are usually associated with low intraocular pressure. The pressure in the affected eye in this

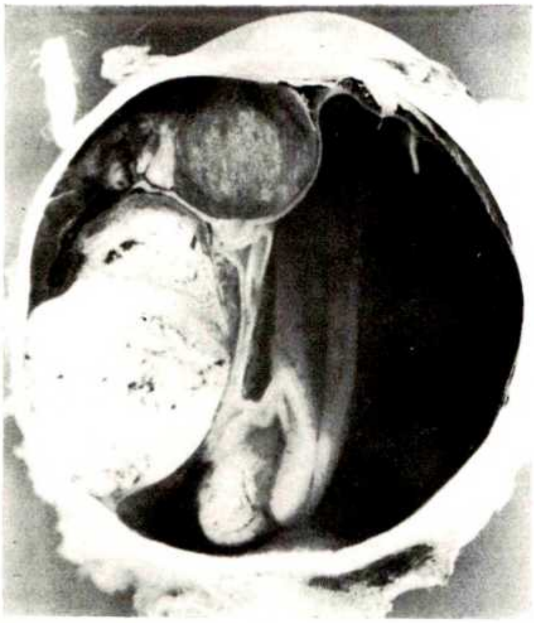

FIG. 2 *Section of globe showing multilobed tumour arising from choroid and ciliary body on temporal side (left) and haemorrhagic retinal detachment on nasal side (right). When viewed through pupil the two lobes looked identical*

case was 10 mmHg compared with 19 mmHg in the other eye. This relative hypotony, however, does not exclude the diagnosis of malignant melanoma. In fact, we have found that most eyes with ciliary body melanomas which have not extensively invaded the anterior chamber angle have lower intraocular pressures than the fellow eye.

The ^{32}P test has recently enjoyed renewed popularity in American ophthalmology (Hagler and others, 1970; Ruiz, 1972; Shields and others, 1974, 1975a; Shields, Annesley, and Totino, 1975b; Shields, McDonald, Leonard, and Canny, 1976c; Shields, Carmichael, Leonard, Federman, and Sarin, 1976a; Shields, Carmichael, Leonard, Sarin, and Federman, 1976b). It may be a highly accurate diagnostic procedure in certain cases of atypical intraocular tumours (Shields and others, 1975a, 1975b; Shields and others, 1976c). We recently reported our results in 300 such procedures (Shields and others, 1976a, 1976b). With the transconjunctival (non-incisional) technique the incidence of false-positive results is less than 1 per cent and the incidence of false-negative results about 4 per cent (Shields and others, 1976a). With the transcleral (incisional) technique there were no false-positive and an incidence of 2 per cent false-negative results (Shields and others, 1976b). We have found it the most accurate ancillary test for differentiating benign from malignant intraocular tumours. It was correct in predicting a malignancy in this case despite the clinical findings, which suggested a choroidal detachment rather than a melanoma. Because the transconjunctival (non-cutting) technique, which produced a positive result, may occasionally be misleading, we incised the conjunctiva for more precise localization. The percentage uptake of the inferotemporal mass over the superior mass (both of which appeared identical clinically) was 561 per cent with one standard counter and 448 per cent with another. Both of these were strongly positive, indicating that the inferotemporal mass was malignant.

Although it has not been our experience, some investigators have stated that false-positive ^{32}P test results may occur with haemorrhagic retinal and choroidal detachments. An intraocular biopsy, therefore, was performed to make certain that the lesion was a melanoma rather than a simulating lesion. We have used this technique successfully in certain difficult cases (Shields, Green, and McDonald, 1973). In this case biopsy confirmed the results of the ^{32}P test and the eye was subsequently enucleated. We do not recommend routine biopsy of suspected posterior uveal melanomas. In fact, biopsy may be contraindicated in such cases (Sanders, 1952; Makley, 1967; Sanders and Smith, 1972). With improved methods for diagnosing intraocular tumours (Shields and McDonald, 1974) biopsy should rarely be necessary.

An important aspect of this case is the diagnostic confusion that occurred. Perhaps the diagnostic difficulties could have been avoided if the patient had been investigated more thoroughly before the cataract extraction. Transillumination, if properly performed, would have shown a shadow corresponding to the tumour inferotemporally. Preoperative ultrasonography would also have detected the mass in this case. At present, however, this technique is often not readily available. As ultrasound becomes more widely used probably tumours will occasionally be detected in the preoperative evaluation of eyes with dense cataracts.

We recommend that visual acuity, transillumination, and ultrasonography findings are carefully evaluated in all patients with opaque cataracts. When a tumour pattern is found a ^{32}P test should be done to confirm or rule out a malignancy. Although the ^{32}P test, when properly performed, is highly accurate in diagnosing intraocular malignancies, therapeutic decisions should not be made solely on the findings. The evidence of ophthalmoscopy, transillumination, fluorescein angiography (Gass, 1974), ultrasonography, antibody studies (Federman, Lewis, Clark, Egerer, and Sarin, 1974), and other procedures must be taken into account before making a definitive therapeutic choice. With this approach, our diagnostic accuracy for intraocular tumours will continue to improve (Shields and McDonald, 1974).

Summary

A case of multilobed malignant melanoma with a haemorrhagic retinal detachment which mimicked a postoperative choroidal detachment is described. Because the lesion showed no resolution six weeks after cataract surgery a tumour evaluation was undertaken. The diagnosis was established with a positive radioactive phosphorus uptake (^{32}P) test and biopsy of the intraocular mass. A suggested approach to the diagnosis in such difficult cases is proposed.

This patient was referred to the Oncology Unit by Dr Narendra Krishna, Coatesville, Pennsylvania. Dr Merlyn Rodrigues performed the pathological examination, and Ms Thea Fischer reviewed the manuscript. Photographic assistance was provided by Mr Terrance L. Tomer and Mr Donald Morozin, and typing by Ms Jean Douglas.

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Retinal microscope

G. MAXWELL STUBBS
From Melbourne, Victoria, Australia

Increasing awareness of retinal degeneration and its significance in the development of retinal detachment has resulted in much more use of indirect ophthalmoscopy, which allows a larger field of view of the fundus and some variation in magnification depending on the power of the condensing lens used. A low power condensing lens provides a larger image, but with conventional instruments this is very unstable. It is usually necessary to accept a smaller image which does not suddenly disappear with slight movements of the lens. A retinal microscope has been developed which overcomes these disadvantages.

Specification

The instrument (Figs 1, 2, 3) provides a stable image of apparent magnification equivalent to that of the direct ophthalmoscope, but with a field of 6 to 7 disc diameters and with all the advantages of binocular viewing. Resolution of the image and stability are more than adequate for routine use in the consulting room or operating theatre. Furthermore, on discarding the condensing lens an operating microscope of 6x, comfortably worn on the head, is immediately available. Thus the need for frequent change from indirect ophthalmoscope to operating loupe is obviated. No adjustment is needed, and from my experience of two years' use the magnification is not too great for the ordinary buckling, scleral resection, and other detachment procedures. An adequate depth of focus is obtained.

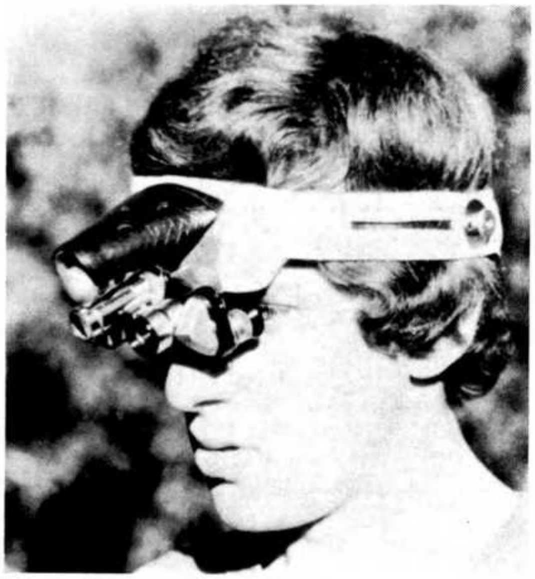

FIG. 1 *Microscope in position*

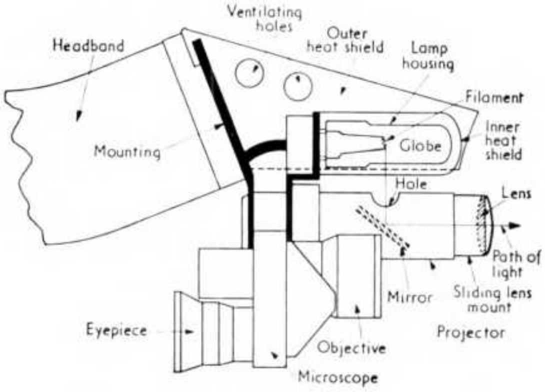

FIG. 2 *Diagram of longitudinal section of instrument*

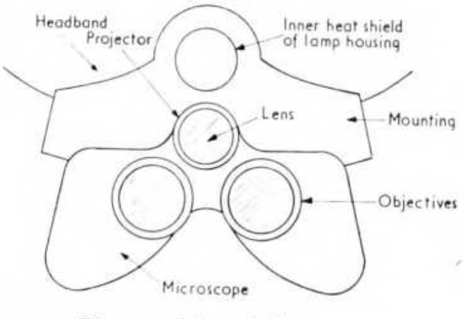

FIG. 3 *Diagram of frontal view*

This arrangement allows detailed examination of areas of retinal degeneration, a difficult task with

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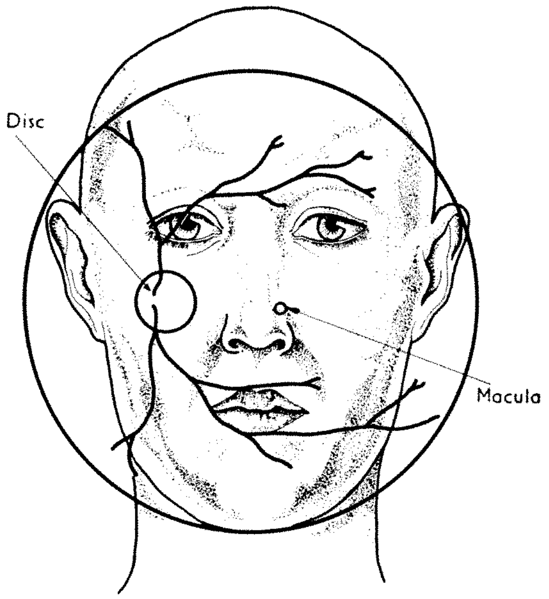

FIG. 4 *Approximate size of fundal image using 20D condensing lens*

conventional indirect instruments, and the great advantage of mobility when used as an operating microscope. The lamp filament may be focused for the increased illumination needed for anterior chamber surgery, but a more diffuse patch of light is quickly obtainable by adjusting the focus, and this provides even illumination of the fundus during ophthalmoscopy. This is possible because of the intense light source of 50W, and it eliminates the annoying patchy illumination produced by conventional instruments. A 20D condensing lens gives bests results (Fig. 4). The quartz iodine lamp produces considerable heat, but suitable ventilation and insulation has been achieved.

The instrument is particularly useful in the consulting room, especially when the condensing lens is held close to the eye. Detailed examination of the cornea and anterior chamber is simply done, and even gonioscopy is possible, with a simultaneous view of the entire angle.

Summary

An instrument is described that provides a stable magnified image for ophthalmoscopy and a low power operating microscope combined to allow greatly improved fundal inspection and to eliminate the need to change instruments during detachment surgery.

I thank Mr Lorimer Fis n and OPSM Melbourne for their help and advice.

The production is currently in the hands of Keeler Instruments Ltd.

Brit. J. Ophthal. (1976) **60,** 392

Book reviews

Anaesthesiology and Resuscitation. By H. Bergmann and B. Blauhut. 1975. Pp. 176, 79 figs, refs. Springer-Verlag, Berlin (no price given)

Four subjects are discussed in this composite volume—anaesthesia in ophthalmology and in ENT surgery, blood coagulation, and blood gas analysis, and they are presented in 'workshop' form. The articles are designed for postgraduate anaesthetists and the ophthalmic section deals with local and general anaesthesia in ophthalmology, the intraocular pressure, and the oculocardiac reflex. The information is up to date and relevant to ophthalmic surgery and this section should be read by those anaesthetists who are concerned with ophthalmic lists. T. J. FFYTCHE

Basic Mechanisms of Ocular Motility and their Clinical Implications (Proceedings of an International Symposium, Wenner-Gren Centre, Stockholm, 4–6 June 1974). Edited by G. Lennerstrand and P. Bach-y-Rita. 1975. Pp. 584, figs, refs. Pergamon Press, Oxford ($60)

This 24th volume in the series records the proceedings of a three-day meeting held in Stockholm in June 1974. It was planned to encourage interaction between the laboratory scientists and clinical investigators, with the scientist first presenting his subject and the clinician discussing the paper and its clinical implications.

The contributors maintain a high standard in their work which concerns the structure and ageing of extraocular muscles, the motor units, and the oculomotor control system. Next, central mechanisms are discussed with particular reference to the vestibulo-ocular reflex, cerebellar influences, and supranuclear ocular motor control. The high quality of the work is maintained in the free contributions which include several papers on the interaction of head and eye movements.

It would be invidious to single out particular authors since nearly all the leading laboratory researchers and clinicians seem to be represented. The aim of interaction between the two groups is not achieved in the written word, although much useful, unreported discussion occurred outside the lecture hall. Nevertheless the intention was right and this book is an excellent account of a wide range of current work into ocular motor problems. Clinicians who read it will be amply rewarded by their increased understanding of some aspects and in a much better position to ask the right questions of the scientists. We may even be able to ask them in the right, scientific language! This, in fact, is the proposed theme of the next symposium. PETER FELLS

The Eye and its Disorders. By P. D. Trevor-Roper. 1974. Pp. 726, figs, refs. Blackwell, Oxford (£11)

This is a reprinting of the 1974 edition, which itself was a new edition of the earlier *Ophthalmology: a Textbook for Diploma Students,* first published in 1955 and subsequently revised in a second edition in 1962. The fact that a reprinting of the third edition of this textbook has been found necessary testifies to its deserved popularity, which in catering for those preparing for the British diploma in ophthalmology meets a need for a clearly written and not too detailed account of the theoretical basis and practical aspects of ophthalmic medicine and surgery.

The first three sections of the book comprising about one-third of its length deal with anatomy, physiology, and optics while the remaining two sections are concerned with diseases of the outer and inner eye.

The aetiology, pathology, and differential diagnosis of all the important ocular disorders are considered and where appropriate details of both medical and surgical treatment are given. The text is highly readable, and the illustrations are clear and add significantly to the value of the book.

The Eye and its Disorders can be recommended to postgraduates beginning the study of ophthalmology as presenting within short compass a succinct account of ophthalmology in sufficient detail to meet the needs of the diploma student or indeed to act as a useful reference text for the interested undergraduate or general practitioner.

Criticisms are slight. Economic necessity has resulted in grouping the colour plates together so that they no longer relate easily to the appropriate text as in the earlier editions of the book, and perhaps one or two of them have been included because of availability rather than because colour adds significantly to their value. The caption to the illustration of 'physiological cupping' in Plate 3 in which the cup to disc ratio is in the region of 0·7 is arguable, and the retinal tear in Plate 4 is the reverse of the usual appearance where the 'arrow' points posteriorly. Inevitably where such a wide range of subjects is dealt with between the covers of one book depth has to be sacrificed, but in general the subject matter is dealt with in sufficient detail to fulfil its remit. Perhaps the section on glaucoma could be improved for although revised it has a slightly outmoded ambience carried over from earlier editions when our understanding of this group of conditions was even poorer than it is at present. One hopes that future editions may find room for recent developments in the understanding of such conditions as disciform degeneration, ischaemic optic neuropathy, and central serous retinopathy.

There is an excellent index and the quality of the paper and the printing is high. The book can be recommended to the postgraduate student beginning the study of ophthalmology both for its authority and its readability. W. S. FOULDS

Genetic and Metabolic Eye Disease. Edited by M. F. Goldberg. 1974. Pp. 654, tables, figs, refs. Little Brown, Boston (£20·30)

The great advances that have been taking place in genetic and metabolic diseases in general have produced a large number of textbooks and monographs on these subjects. Ophthalmologists have been in the forefront of research into clinical genetics ever since its emergence as a subject in its own right at the beginning of the century. During the past 20 years there have been relatively few books devoted to ophthalmic genetics and this excellent publication is, therefore, particularly welcome. While every chapter has much to offer the reader, several have been singled out for particular mention, either because of their clinical value or because they are a reflection of the reviewer's particular interests.

Part One is devoted to 'Methods of study in genetic eye disease'. It includes a chapter by George Spaeth on the carrier state and lists more than 60 conditions with ophthalmic manifestations in which the carrier state can often be detected by a biochemical abnormality or an abnormal clinical appearance. Since this chapter was written, the list could probably be considerably enlarged. Fraser discusses the aetiology of severe visual handicap in childhood, a subject which is at last receiving the attention it deserves. It is apparent from his discussion of acquired and genetically-determined causes that there is still much we have to learn about this topic. In a comprehensive and extremely useful chapter Berman describes genetic and metabolic eye diseases and their biochemical diagnostic tests. To illustrate the recent advances that have occurred in this subject, only 2 per cent of the 322 references are over 10 years old.

Part Two is concerned with 'Genetic determination of clinical eye disease'. Bron and Tripathi review the isolated corneal dystrophies and those associated with systemic and with genetically-determined disorders. There is a strong emphasis on the clinical appearance of the cornea in these various conditions, making this chapter particularly valuable to the practising ophthalmologist. The macular dystrophies are ably discussed by Deutman who has finally laid to rest the monistic view of this group of disorders. Until these lesions can be classified biochemically, their morphological classification, as presented here, will be the most useful clinically. The complex group of heredofamilial disorders of the optic nerve has been ably handled by Glaser while the rapidly growing topic of chromosome deletions and eye disease is discussed by Howard.

Part Three, 'Therapy and prevention of genetic eye disease', consists of chapters on therapeutic principles by Cotlier, ocular pharmacogenetics by Lieberman, and genetic counselling by Irene Maumemee. This is by far the shortest part of the book, but one which could hardly have been envisaged a few years ago. It is hoped that a section such as this written in 10 years' time will be very much larger.

The editor is to be congratulated on producing such a valuable book covering one of the fastest growing areas of ophthalmology. It can be highly recommended to all ophthalmologists for repeated perusal, and should be obligatory reading for all those studying for higher degrees.

BARRIE JAY

More Help for Dyslexic Children. By T. R. MILES and E. MILES. 1975. Pp. 74, figs, refs. Methuen, London (£1·20)

Developmental dyslexia, or congenital word-blindness as it was then called, was first anticipated in 1896 by a Glasgow eye-surgeon—Dr James Hinshelwood. Actually the very first case of this kind was described by the father of the Emeritus Ophthalmic Surgeon to Guy's Hospital, Mr Gayer Morgan. Because of the nature of the presenting symptom, namely inability to make head or tail of printed or written words, it is not surprising that visuoperceptual errors were queried. The early literature upon this subject was largely made up of case reports published by distinguished ophthalmologists, mainly British, among whom the names of Nettleship, Thomas, Hubert Fisher, Treacher Collins, Stephenson, and Doyne are conspicuous. Later, the focus of attention switched to neurologists who nowadays visualize a genetically-determined localized form of delayed maturation within the learning-process.

In some places, mostly in the United States of America, ophthalmologists for a time renewed their interest in dyslexia, some of whom postulated that a disorder in the eye movements during the act of reading was responsible for retardation in reading, to be cured by courses of eye-exercises. Fortunately, that particular heresy never reached this country and is on its way out in America.

Many eye specialists, however, still see these cases in the early stages and are intrigued thereby, for dyslexia cannot be diagnosed until all perceptual errors have been eliminated.

To those who are interested in this topic, this simple book—and particularly the first two chapters—may be warmly recommended.

M. CRITCHLEY

Ophthalmic Electrodiagnosis. By N. R. GALLOWAY. Vol. 1, Major Problems in Ophthalmology, edited by P. D. TREVOR-ROPER. 1975. Pp. 169, figs, tables, refs. Saunders, Philadelphia (no price given)

Ophthalmologists are in a privileged position among clinicians because the eye is readily accessible for inspection and there are many reliable and sensitive tests of function. It is probably for this reason that electrical methods of investigation have not achieved the wide application apparent in other disciplines. The electrical responses of the visual system were discovered more than a century ago and their study has been most valuable in physiological research. Much basic information has been acquired but unfortunately many of the contemplated diagnostic prospects have proved disappointing because they are less sensitive than established techniques. On the other hand there is a special field in which these methods have a vital use. Many clinicians are unaware of the scope and even of the existence of some of these tests, possibly because of the lack of a clinically orientated description. This book is an attempt to fill this gap.

The first half of the book comprises a glossary of basic electronic terms, the physiological bases of the various retinal tests, and a brief, and perhaps irrelevant, note on other tenuously related investigations.

The second half of the book is devoted to clinical investigations. It is introduced by a chapter on the organization of an electrodiagnostic clinic and the methods of recording normal response. The rest of the section discusses the results of such tests in various ocular diseases.

This book will fulfil the needs of most ophthalmologists who wish to understand the place of electrodiagnosis in contemporary ophthalmology. A valuable feature is the list of references at the end of each chapter. Apart from a superficial discussion of cortical responses there are numerous deliberate omissions in the application of retinal tests because these are not of great clinical value.

Many illustrations have been drawn to explain certain points and in general they are clear and useful but Fig. 7·1 does not make clear the enormous amplitude as well as time difference of the EOG and ERG. The clinical ERG traces may also be misleading. The author uses a high intensity stimulus and this, together with the effect on the ERG waveform, is noted in the text. Unfortunately the reader may miss this point and find it difficult to equate some of the author's traces with those in the literature using more conventional stimuli.

Ophthalmic electrodiagnosis is generally accepted to date from 1945 with Karper's monograph although excellent earlier studies had appeared. In the 30 years since then extensive studies have been published and a very active international society has helped the development of the various techniques. It is never safe to say that further major development will not occur but it would seem that the indications and applications of tests of retinal function are fairly clearly established. It is this aspect of visual electrophysiology to which the book is almost entirely devoted. A future edition will no doubt be more concerned with cortical electrical responses. J. H. KELSEY

The Perception of Colour. By R. M. EVANS. 1974. Pp. 248, figs, tables, refs. Wiley, Chichester (£9·95)

Evans wrote a standard work on colour a quarter of a century ago, and in this posthumous publication he stresses the dissatisfaction he experienced in trying to organize basic colour-matching data in terms of stimulus parameters. This is why he wanted to put forward a design for a new system, called 'perceptual colorimetry'. Classical 'stimulus colorimetry' is a sharp tool, perfected for the protection of manufacturers but it is uninformative when it comes to communication on the subjective experience of colour. This is what he tried to remedy in this book.

Few other works on this subject cope without some coloured illustrations, and none with only 13 diagrams and a description of the structure of the eye by the printed word alone. Evans nevertheless manages to get across his message, which is, basically, that conventional colorimetry represents an unrealistic abstraction. He is much concerned with simultaneous contrast and with surface attributes, since what matters to him is colour as he perceived it. We rarely see colours in the isolation enforced by a colorimeter, however sophisticated it may be in concept. Evans was emphatic about the inadequacies of standard systems, yet, true physicist that he was, he believed in the possibility of a standard observer.

Evans takes tentative steps to deal with adaptation but seems wholly ignorant of the work done on this aspect of perception by R. W. G. Hunt and others. While he sees the difficulty associated with ingrained terminologies, he is as baffled by object colours as Aristotle was. However, Evans had an advantage over the Greek philosopher; he could (but does not seem to) have conversed with physiologists. He would have learnt that the very crystalline lens which he believed to image the outside world on to the retina makes impossible a standard study or a universally valid system. R. A. WEALE

Notes

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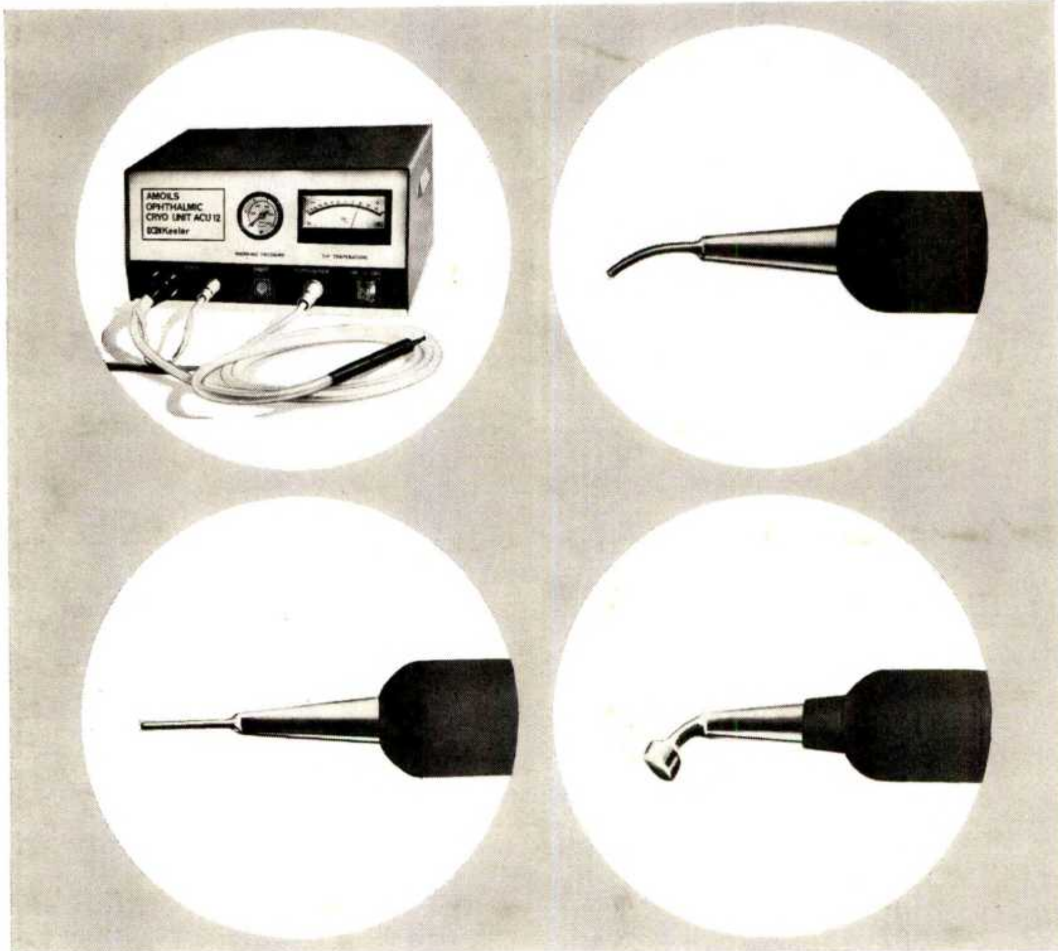

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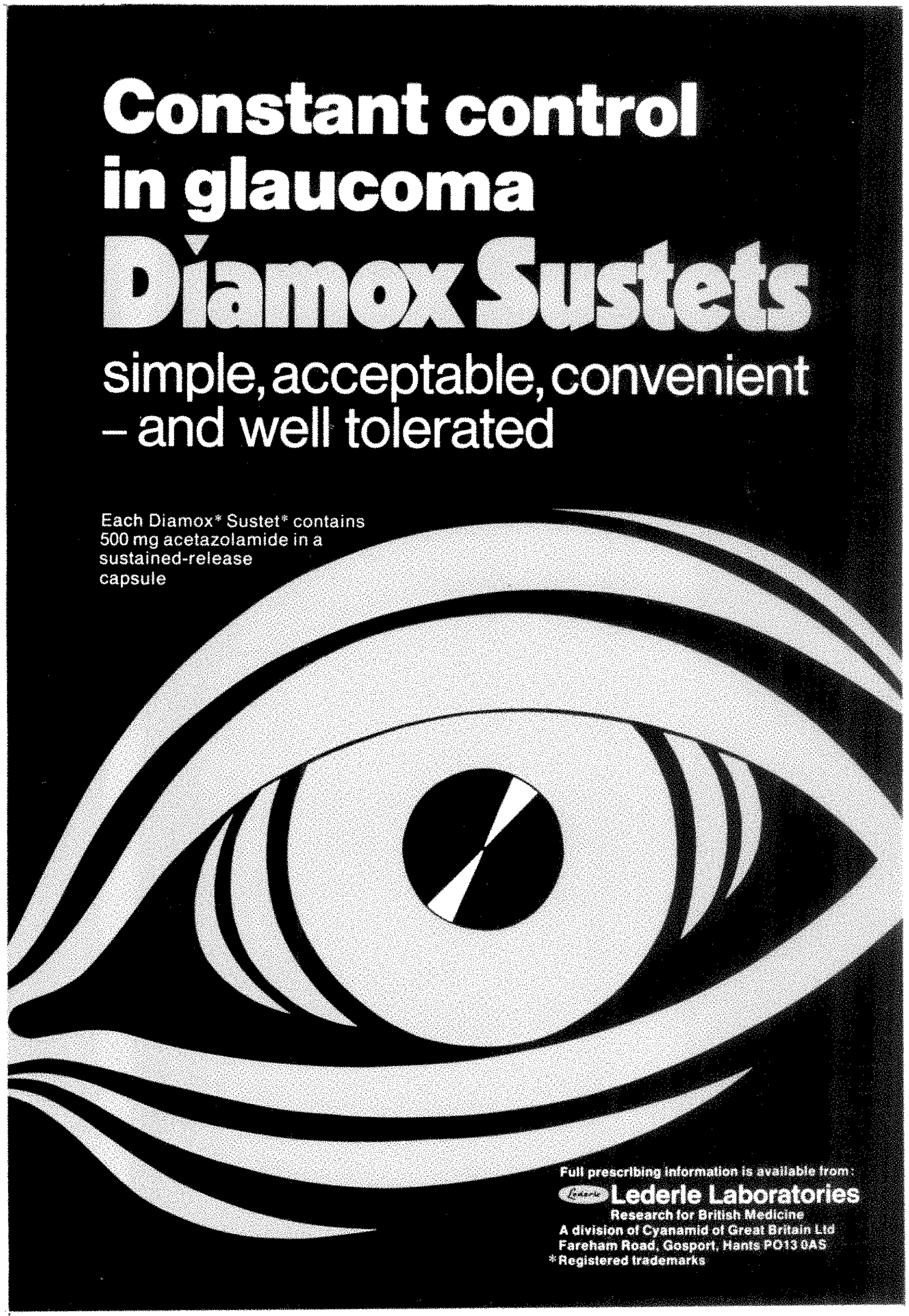

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Professor S. Chandran (Malaysia)
Dr Hung Cheng (U.K.)
Professor Ian Constable (Australia)
Dr Richard L. Cooper (Australia)
Dr R.D. Dhanda (India)
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Dr David J. McAuliffe (Australia)
Professor Aly Mortada (Egypt)
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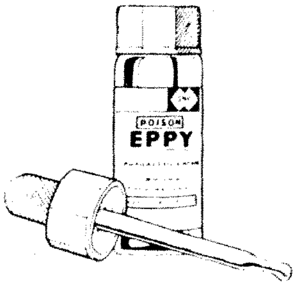

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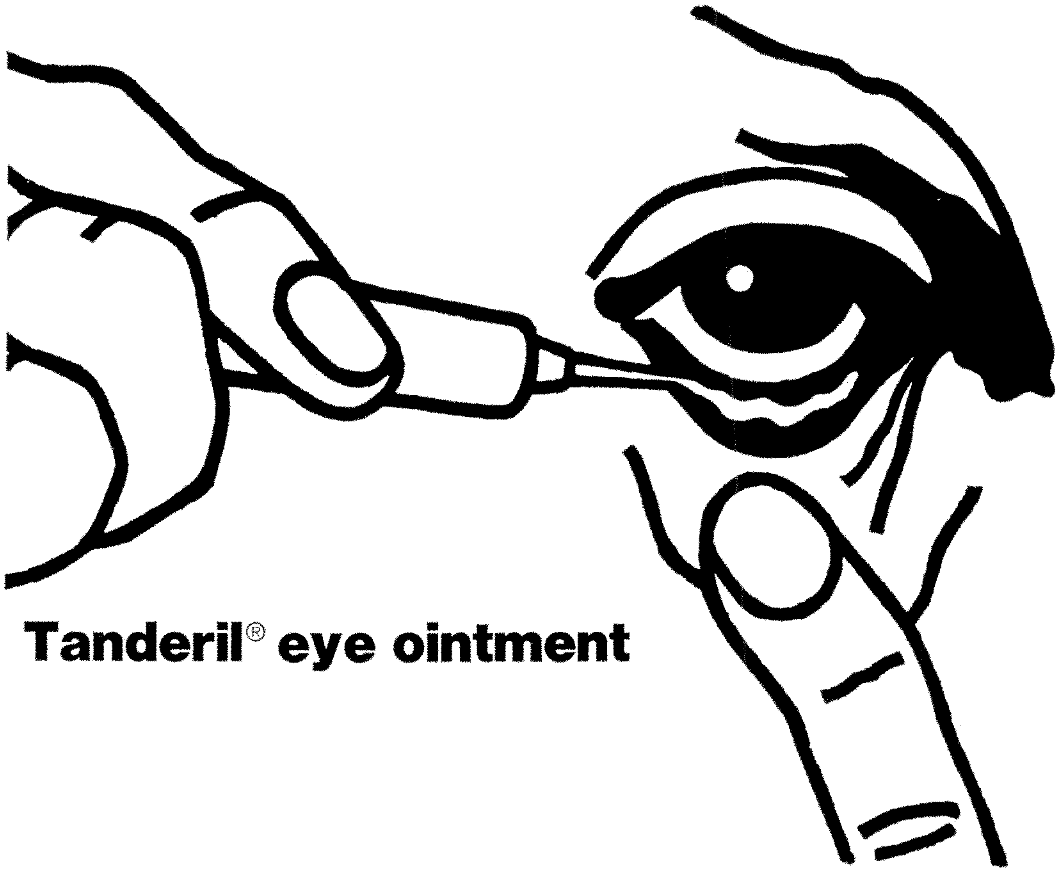

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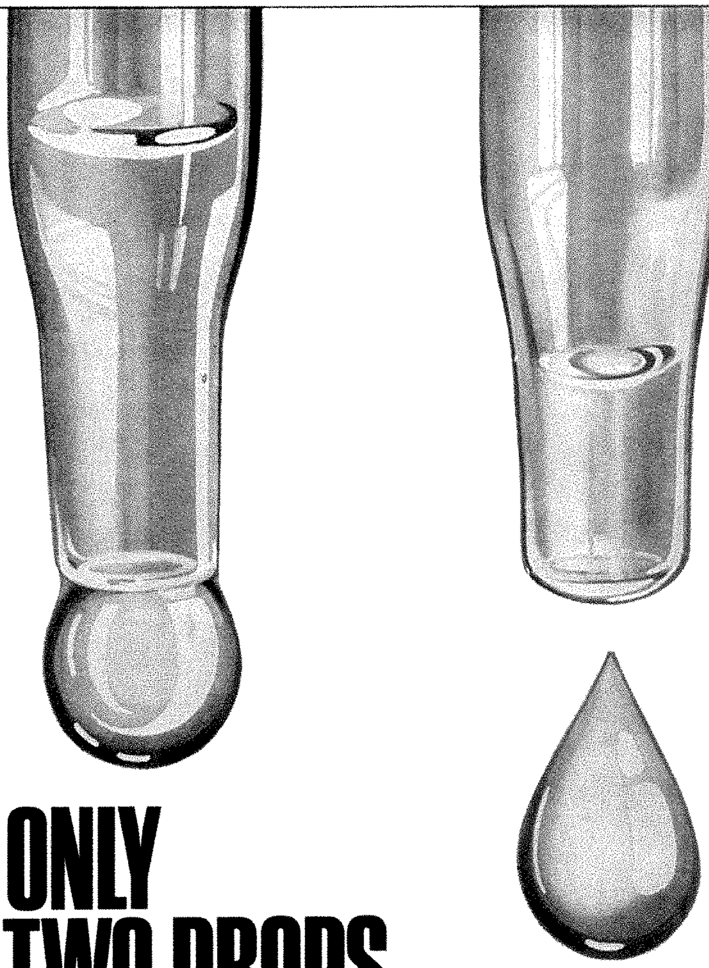

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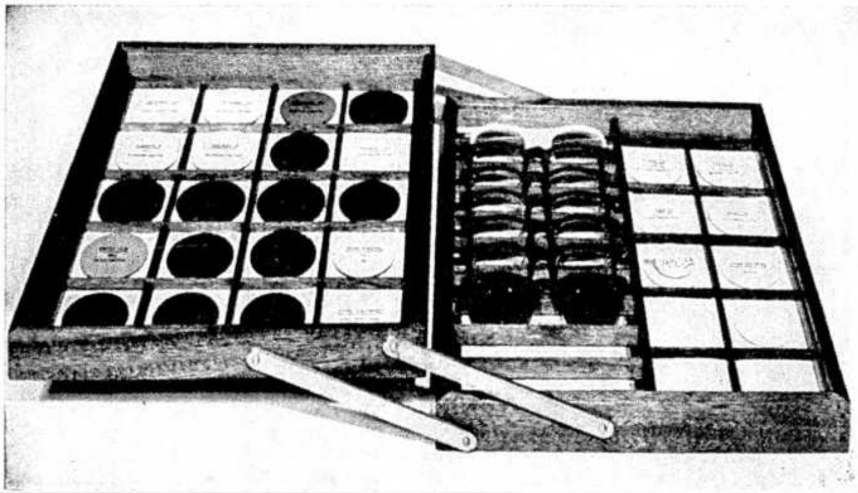

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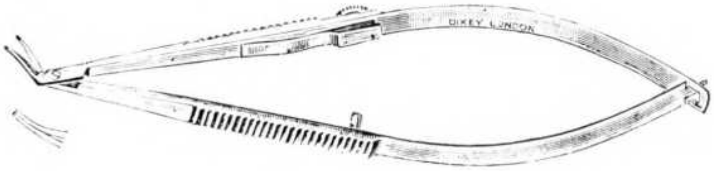

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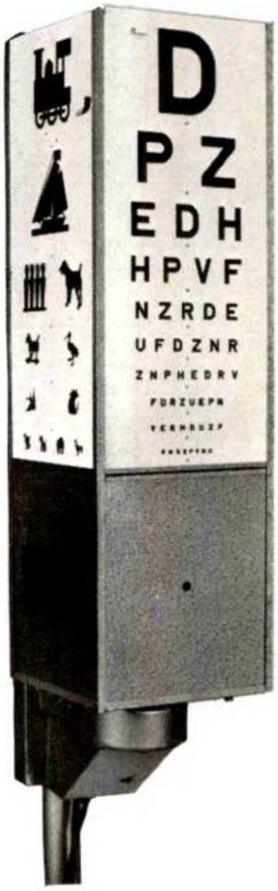

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Brit. J. Ophthal. (1976) **60**, 395

Editorial: Retinal venous obstruction

Retinal vascular occlusion disease is a significant cause of visual loss in the United Kingdom (Sorsby, 1966), and yet there is uncertainty concerning several aspects of retinal venous obstruction which represents a considerable proportion of this disease group. Three papers in this issue are concerned with this subject.

The factors which precipitate venous obstruction have yet to be precisely defined. As recently as 1965 Hayreh concluded, as a result of animal experiments, that central retinal arterial obstruction was an essential prerequisite for venous obstruction to produce the familiar clinical appearance of 'central retinal vein occlusion' (Hayreh, 1965); three years later Fujino, Curtin, and Norton (1968) indicated that this was not necessarily the case. Histopathological studies demonstrated structural changes in the retinal arteries supplying the segment affected by branch retinal occlusion (Rabinowicz, Litman, and Michaelson, 1968), but it has been shown clinically that arterial changes occur progressively after venous obstruction rather than predating the event (Kohner and Shilling, 1976). The density of visual field loss in retinal branch vein obstruction has been adduced as evidence of coexisting retinal arterial disease (Birchall, Harris, Drance, and Begg, 1976), and yet profound atrophy of the inner retina occurs in monkeys after experimental occlusion of the retinal veins only (Hamilton, Marshall, Kohner, and Bowbyes, 1975).

McLeod and Ring (page 419) report the interesting observation of infarction of retinae supplied by cilio-retinal arteries in 10 patients with central vein occlusion. While acknowledging that there may be several explanations for this phenomenon they conclude that there was probably pre-existing disease of the cilio-retinal supply, although there is little firm evidence to support this. It is equally possible that in some patients the cilio-retinal supply is more affected by raised retinal venous pressure than the central retinal artery supply. In central vein occlusion the peripheral resistance of the whole of the central arterial system is raised, yet this affects only a small part of the ciliary system. In patients whose cilio-retinal arteries arise from the posterior ciliary arteries near the globe or even within the choroid itself this may be particularly relevant. Blood destined for the cilio-retinal arteries may be shunted through the choroid and this may be more pronounced if there is reactive dilatation of the choroidal vessels in response to retinal ischaemia after central vein occlusion.

There is similar uncertainty concerning the changes occurring at the site of obstruction. It has been suggested by many authors that thrombosis was the cause of obstruction in the retinal vascular outflow. However, histological studies have failed to show this and have indicated that the venous lumen was compromised by the swelling of the endothelial cells and of tissue in the inner venous walls in both branch (Seitz, 1964) and central retinal vein obstruction (Klien, 1953; Klien and Olwin, 1956); focal leakage of dye into the venous wall identified during fluorescein fundus angiography is likely to be the clinical correlate of this histological change in branch vein occlusion (Clemett, 1974). In discussions concerning pathogenesis of venous occlusion, little attention has been paid to the importance of changes in constituents and physical properties of blood; the paper by Ring, Pearson, Sanders, and Wetherley-Mein (page 397) concerns this aspect. This is particularly important since venous drainage is probably never completely obstructed in retinal venous occlusive disease, but continues, through a high resistance system of a partially obstructed lumen in the principal vein or of by-pass channels. Under such circumstances blood viscosity would critically influence the importance of such obstruction to circulatory changes. By measuring whole blood and plasma viscosity they have demonstrated higher values in patients with central retinal vein occlusion than in a comparison group. This disparity was greater at low shear than at high shear rates, which, as the authors point out, may be the more relevant when considering venous flow. The full significance of this finding has yet to be appreciated, but it certainly deserves greater attention and further investigation.

It is acknowledged that the visual prognosis in retinal venous obstruction is variable, in that some patients suffer profound visual loss while others regain their sight completely. The uncertainty concerning the visual outcome poses difficult problems for the clinician when giving a prognosis to the patient. The advent of photocoagulation as a possible method of treatment of retinal venous obstruction has highlighted this defect in our knowledge. It has made it difficult to identify those patients who need treatment because of poor visual prognosis, and impossible to make even a rough estimate of the efficacy of treatment before completing a randomized clinical trial. Ring and others (1976) have also turned their attention to the relevance of blood and plasma viscosity to the evolution of retinal vascular changes after central retinal vein obstruction. They found significantly higher values in patients who developed large areas of retinal capillary non-perfusion and therefore poor visual prognosis when compared with those who maintained good retinal capillary perfusion. Laatikainen and Kohner (page 411) present results of a prospective study by which the value of fluorescein fundus angiography has been assessed in predicting the visual prognosis of central retinal vein occlusion. Extensive capillary closure one month after the initial symptoms indicated a poor visual prognosis progressing to blindness, extensive leakage and a broken capillary arcade at the fovea indicated a low chance of recovery of visual acuity, while absence of these changes was associated with good visual outcome. Both these papers present information by which the visual prognosis may be determined more accurately in patients with central retinal vein obstruction. The current enthusiasm for photocoagulation highlights the importance of these findings which may be paramount when assessing the need for treatment and in the design of treatment trials.

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Brit. J. Ophthal. (1976) **60**, 397

Viscosity and retinal vein thrombosis

C. P. RING,* T. C. PEARSON,† M. D. SANDERS, AND G. WETHERLEY-MEIN
From the Departments of Ophthalmology and Haematology, St Thomas's Hospital and Medical School, London

Retinal vein occlusions (RVO) have been well documented since Leber (1877) and Michel (1878) first described branch and central retinal vein occlusions respectively. However, no further progress was made until Novotny and Alvis (1961) introduced fluorescein angiography, which demonstrated the phenomenon of capillary non-perfusion, found in some cases of RVO, and gave investigators a useful tool for trying to determine the pathophysiology of the condition. A direct role for arterial occlusion in producing the clinical features of RVO has been discounted (Kohner and Shilling, 1976), but arterial disease is generally agreed to have a significant role in the aetiology. Although a much debated point, a complete thrombotic occlusion of the vein is generally thought not to occur. The pathological process at the site of the occlusion consists of changes in the vessel walls, blood constituents, and blood flow. These three components of Virchow's triad are interrelated, and changes in the vessel wall and blood flow have been investigated in man and animals by techniques of pathology (Rabinowicz, Litman, and Michaelson, 1968) and by angiography (Kohner, Dollery, Shakib, Henkind, Paterson, de Oliveira, and Bulpitt, 1970; Fujino, Curtin, and Norton, 1968). The importance of the effect of the blood constituents on the blood viscosity has received little attention, although Begg (1969) suggested this as a useful area of investigation.

Viscosity may be defined as the friction between two moving planes of fluid. Mathematically it may be defined as the ratio of the applied force (shear stress) to the differential velocity of the two planes (shear rate). For simple fluids the rate of flow is directly proportional to the applied force (Newtonian behaviour). Blood, however, does not show this simple relationship and is termed non-Newtonian. Therefore when measuring whole-blood viscosity, as in the present study, a wide range of shear rates must be used in order to include all those which might be met in a normal or pathological circulation. Cone-plate and coaxial cylindrical viscometers have been widely used in this and other studies of whole-blood viscosity because the shear rate can be accurately monitored. The viscosity of plasma, which may be considered to behave in a Newtonian fashion (Dintenfass, 1971), may for this reason be accurately measured in a capillary viscometer in which the shear rates are inconstant, and this technique has also been used in the present investigation. Yield stress of a material under shear is the applied force necessary to overcome frictional forces between the sliding planes and so induce movement (Whitmore 1968). Blood has been shown to exhibit this rheological property (Merrill, Margetts, Cokelet, and Gilliland, 1965) and therefore the role of yield stress was also investigated.

Increased blood viscosity is associated with various pathological conditions in which vascular thrombosis or occlusion is a feature. Suggested associations are postoperative deep vein thrombosis (Dormandy and Edelman, 1973), recent cerebral infarction (Ott, Lechner, and Aranibar, 1974), acute myocardial infarction (Burch and De Pasquale, 1963), hypertension (Tibblin, Bergentz, Bjure, and Wilhelmsen, 1965), angina (Dormandy, 1975), and diabetes (Ditzel, 1967). The role of blood viscosity in retinal vein occlusion seems to have received little attention apart from the restricted studies of McGrath, Penny, Wechsler, and Hunyor (1973). The present study was designed to examine the role of viscosity and blood flow in the aetiology of retinal vein occlusion and the development of capillary non-perfusion.

Patients and methods

Forty-four unselected patients with retinal vein occlusions (Table I) attending the eye department, St Thomas's Hospital, were investigated. The group consisted of 25 men and 19 women with a mean age of 61·6 years (range 40–76). Twenty-three of the patients were investigated within the first week of presentation and 15 within a further four weeks. In six cases, however,

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*Research fellow supported by the Prevention of Blindness Research Fund

†Merchant Taylor's research fellow

Address for reprints: Dr C. P. Ring, Moorfields Eye Hospital, City Road, London EC1

Table I *Summary of the 44 patients with retinal vein occlusion investigated*

Patients	*Central retinal vein* (n=20)	*Branch vein* (n=24)
Women	9	10
Men	11	14
Mean age (years)	62·5	60·7

the patient was unaware of symptoms and the diagnosis was made on ophthalmoscopy.

The group was compared with a group of 30 controls consisting of 18 men and 12 women with a mean age of 57·9 years (range 45–75) taken from hospital personnel and ophthalmic patients who had neither inflammatory nor vascular conditions of the eye. Possible controls with any history or evidence of hypertensive, cardiovascular, or respiratory disease were rejected. A younger control group of 30 hospital personnel (mean age 30·7 years; range 20–44) was also examined but the results were not used for statistical comparison with the RVO group for reasons discussed later.

COLLECTION AND PREPARATION OF BLOOD

Blood samples were taken without venous occlusion during sampling and at the same time of day (1400 ±1 hour) from both the controls and the patients, who were ambulatory immediately before venesection. The samples were subdivided for estimation of whole blood and plasma viscosity, fibrinogen, haematological examination, and biochemical analysis.

VISCOSITY MEASUREMENTS

These were carried out within seven hours of collection on lithium heparinized blood (20 U/ml) which was mixed continuously at room temperature during the interval before measurement. Whole-blood viscosity was measured at four shear rates. A Wells Brookfield cone-plate micro-viscometer (Model LVT) was used to measure viscosity at a shear rate of 230 inverse seconds (s^{-1}). A Contraves Low Shear 2 co-axial cylindrical type viscometer was used for measurements at shear rates of 23, 2·62, and 0·77 s^{-1}. Plasma viscosity was measured with a Harkness Mk 2 capillary viscometer. All measurements were made at 37°C against a standard control (Brookfield viscosity standard). Estimations were all duplicated and the mean value taken.

Yield stress values were obtained by constructing a Casson plot (Casson, 1959) of the square root of the shear stress against the square root of the shear rate. Using shear stress values calculated at shear rates of 2·62 s^{-1} and 0·77 s^{-1} a line was extrapolated which gave the yield stress where the Y axis was intercepted. Merrill and others (1965) suggested that a straight linear relationship did not hold for values of shear rate less than 1 s^{-1}, but thought that this was probably owing to difficulty in interpreting viscosity results at low shear rates. We found, in separate experiments, that with the Contraves LS2 viscometer, which has a rapid response time, the relationship was linear to values of shear rate less than 1 s^{-1} (down to 0·488 s^{-1}).

HAEMATOLOGICAL INVESTIGATIONS

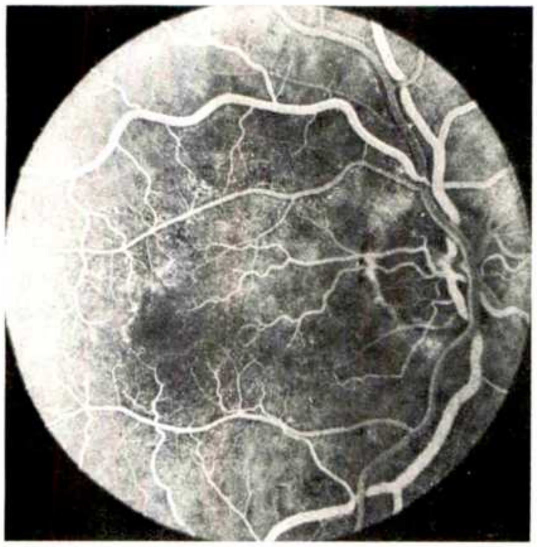
Routine haematological values were measured on a Coulter Counter Type S apparatus and platelet counts on a Coulter Counter Type Fn. Particular attention was paid to the packed cell volume (PCV), which was measured separately by us by a microhaematocrit technique in the heparin samples used for whole-blood viscosity measurement. Trapped plasma was measured on a further heparin sample by a ^{125}I-labelled albumin dilution technique (Garby and Vuille, 1961). Observed PCVs were adjusted to the correct PCV by subtracting the measured trapped plasma value. A blood film in each case was examined by one of us (TCP). ESR was measured at one hour by the Westergren method. Plasma fibrinogen was measured by the method described by Ingram (1952).

CHEMICAL DETERMINATIONS

Serum protein, uric acid, and creatinine levels were determined by a routine multichannel analyser (Technicon SMA 12/60). Immunoglobulins (IgG, IgA, IgM) were estimated using immunodiffusion plates. RVO patients also had routine investigation of serum cholesterol, antinuclear factor, and serum complement. Fasting plasma triglycerides were estimated and a glucose tolerance test was carried out within the next week.

Table II *Classification of 44 RVO patients into three groups (A, B, C) on the basis of the fluorescein angiographic appearances of the retina. The modified classification of branch vein occlusion as suggested by Archer and others (1974) is shown for comparison*

RVO group classification	*BVO classification (Archer and others)*	*Definition*	*CRVO*	*BVO*	*Total*
A	1 2	No significant areas of retinal ischaemia	12	5	17
B	3, subgroup A	Focal areas of capillary non-perfusion	2	5	7
C	3, subgroup B 4	Extensive areas of capillary non-perfusion	6	14	20



(1*a*)

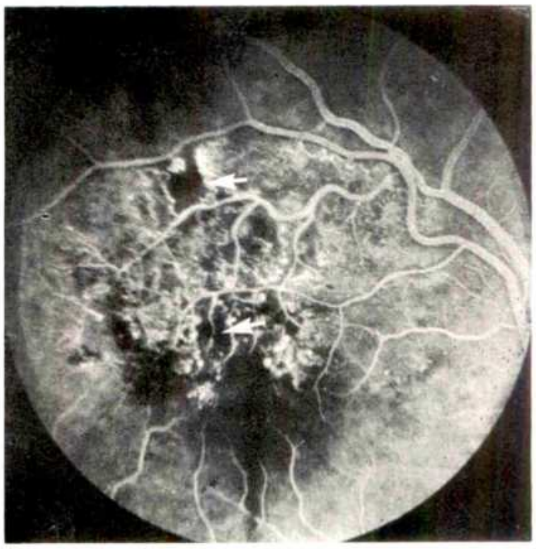


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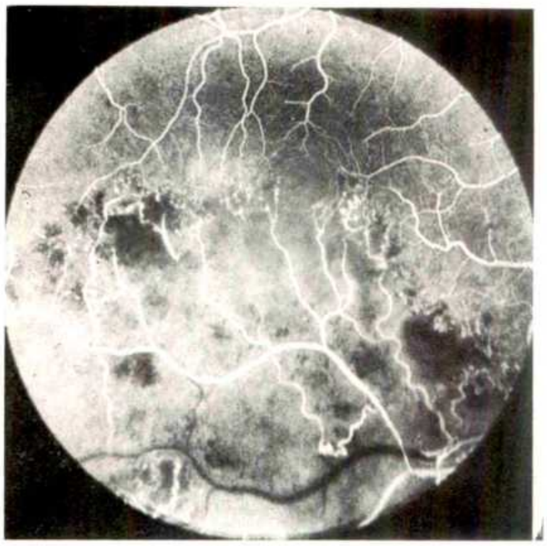
FIG. 1 *Branch vein occlusions.* (a) *Group A. Dilated capillaries in distribution of a small superior temporal occlusion.* (b) *Group B. Small areas of capillary non-perfusion (arrows) in a superior temporal occlusion.* (c) *Group C. Widespread capillary non-perfusion in an inferior temporal occlusion. Note irregularity of calibre and leakage from arterioles passing through area*



(1*c*)

BLOOD PRESSURE

When each subject was first seen the blood pressure was taken with the patient seated and by the same investigator (CPR). Diastolic pressure was taken as the point of muffling of Korotkoff's sounds. Blood pressure differential between the two arms was excluded in the RVO group. Patients with a diastolic pressure above 95 mmHg were considered to be hypertensive.

OPHTHALMIC EXAMINATION

Every patient in the RVO group was assessed on each visit with measurements of corrected visual acuity, slit-lamp examination, and applanation tonometry. Colour photographs (Kodachrome II) were taken and fluorescein angiography performed at presentation and on at least one other occasion. For fluorescein angiography 5 ml of 20 per cent sodium fluorescein was injected into an antecubital vein and the transit of dye through the fundus was recorded at 1-second intervals with a Zeiss fundus camera (Ilford FP4 film).

For ethical reasons fluorescein angiography was not performed on the control group.

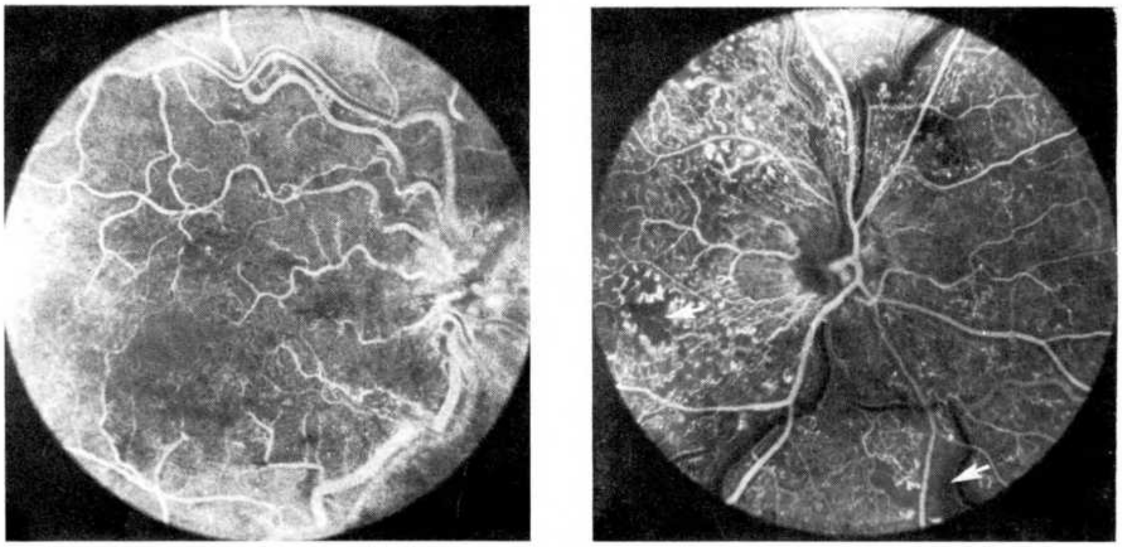
STATISTICS

Student's *t* test was used for comparisons of the groups.

Results

GROUPING RVO PATIENTS

Archer, Ernest, and Newell (1974) classified their branch retinal vein occlusion (BVO) patients into four major groups (1–4), subdividing group 3 into 3A and 3B according to the results of a number of investigations by fluorescein angiography and suction cup ophthalmodynamometry. We have included both central and branch vein occlusions, which are considered to have similar underlying pathology. We have used a simplified classification to subdivide the whole RVO group purely on the



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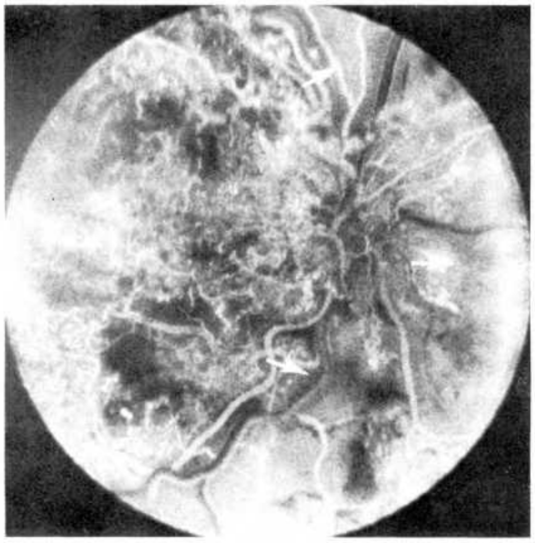

(2*c*)

FIG. 2 *Central vein occlusions.* (a) *Group A. An intact capillary bed with widespread dilatation.* (b) *Group B. Small areas of capillary non-perfusion (arrows).* (c) *Group C. Extensive capillary non-perfusion (arrows)*

fluorescein angiographic appearances, which were assessed for the presence and extent of capillary non-perfusion. Table II shows how the 44 RVO patients were subdivided into three groups, with the definitions and classification of Archer and others (1974) shown for comparison. Figs 1 and 2 are fluorescein angiograms illustrating an example of each subdivision in branch vein occlusion and central vein occlusion respectively.

Although all care was taken, an obvious source of inaccuracy with this method is observer error in assessing the capillary non-perfusion. All patients were subdivided before the significance of the viscosity results was known. Subsequent statistical comparison of the RVO group was made in order to eliminate observer error—that is, group A was compared against group C, then groups A and B against group C, then groups B and C against group A.

VISCOSITY MEASUREMENTS

Whole-blood viscosity measured on the collected blood samples (that is, at the observed PCV) showed no statistical difference between the total retinal vein occlusion group and the control groups, at all shear rates. However, there was a highly significant difference ($P < 0.01$ at 230 s^{-1} and $P < 0.001$ at 23, 2·62, and 0·77 s^{-1}) between the control group and those patients with large areas of capillary non-perfusion (group C). Analysis within the RVO group itself showed a highly significant statistical difference between group A and group C ($P < 0.001$ at all four shear rates). Combination of group B with either A or C made little difference ($P < 0.001$ in six of the analyses and $0.001 < P < 0.005$ in the other two). Fig. 3 illustrates the viscosity results in the RVO and control groups at shear rates of 230 s^{-1} and 0·77 s^{-1}.

These findings indicate that the whole-blood

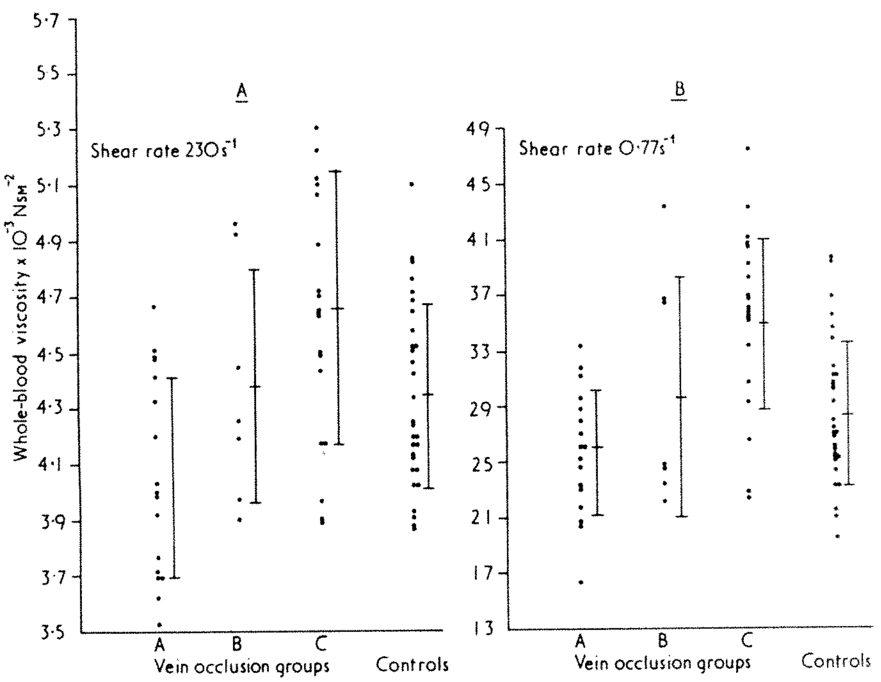

FIG. 3 *Whole-blood viscosity results of RVO groups and controls at PCV at presentation at* (a) *shear rate of* 230 s^{-1}, *and* (b) *shear rate of* 0·77 s^{-1}. *Mean and one standard deviation are indicated* ($P <$ 0·001 *for difference between groups A and C*)

viscosity measured at the observed PCV was abnormal only in the RVO groups with capillary non-perfusion. If the RVO group is taken as a whole the abnormality was concealed by the normal viscosity of RVO patients without capillary non-perfusion.

Dormandy (1970) introduced the idea of using a regression line relating log viscosity values and PCV to 'correct' the viscosity results at the observed PCV to viscosity values at a mean PCV level. This eliminates the dominant PCV influence on whole-blood viscosity and allows analysis of the other major influencing factors, plasma protein composition and red cell deformability. Mean PCV values for the control and retinal vein occlusion groups were 0·431 and 0·426 respectively. Viscosity results were 'regressed' to a PCV of 0·42, which allows for deducting 0·005 for trapped plasma. Comparison of whole-blood viscosity in the RVO group against the control group at this PCV level showed that it was higher in the occlusion group. Although this difference was not statistically significant at a shear rate of 230 s^{-1} ($0{\cdot}05 < P < 0{\cdot}1$) it became increasingly significant at lower shear rates ($0{\cdot}005 < P < 0{\cdot}01$ at 23 s^{-1}; $P = 0{\cdot}001$ at 2·62 s^{-1}; and $0{\cdot}001 < P < 0{\cdot}005$ at 0·77 s^{-1}). Investigations within the RVO group on this basis showed a statistically significant difference ($0{\cdot}01 < P < 0{\cdot}02$) between the closure/non-closure groups at shear rates of 0·77 s^{-1} and 230 s^{-1} ($P = 0{\cdot}025$). The results at 23 s^{-1} and 2·62 s^{-1} were higher but not statistically significant ($0{\cdot}05 < P < 0{\cdot}1$). Fig. 4 shows the regressed viscosity results of the RVO and control groups at shear rates of 230 s^{-1} and 0·77 s^{-1}.

These results show that after the PCV effect on whole-blood viscosity had been eliminated other factors still influenced the results. The viscosity results for the total RVO group were higher than the control group. The patients with capillary non-perfusion had higher viscosity values than those without capillary non-perfusion.

Yield stress values were calculated from whole-blood viscosity measurements made at the observed PCV and there was no significant difference between the total RVO and control groups. However, analysis of group C against the controls showed a significantly higher yield stress value in group C ($P < 0{\cdot}001$). When the RVO patients were considered significantly higher yield stress values were found between groups A and C ($P < 0{\cdot}001$) and the statistical significance remained unaltered whether group B results were included with those of group A or C. Fig. 5 shows the yield stress values of these three groups and the controls for comparison.

These findings indicate that the yield stress calculated on the viscosity results at the observed PCV was abnormal in RVO patients with capillary non-perfusion. Taken within the RVO group as a whole this abnormality was concealed by the normal values of those without capillary non-perfusion.

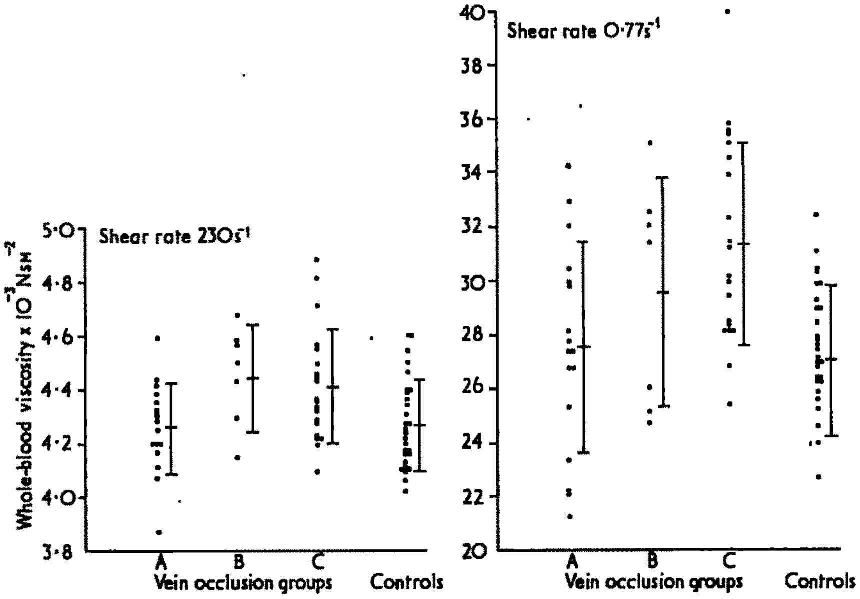

FIG. 4 *Whole-blood viscosity results in RVO and normal groups, after regression of viscosity results to a mean PCV of 0·42, at (a) shear rate of 230 s^{-1}, and (b) shear rate of 0·77 s^{-1}. Mean and one standard deviation are indicated* (0·01<P<0·02 at 0·77 s^{-1}; P=0·025 at 230 s^{-1} *for difference between groups A and C*)

After regression of the whole-blood viscosity values to the mean PCV (0·42) the yield stress values were recalculated, and there was no difference between the results of the control and total RVO groups. However, there was a highly significant difference (P<0·001) when group C was compared with the controls and also when the three RVO groups were analysed. Patients in group C had higher yield stress values than those in group A. Fig. 6 shows the yield stress values in the RVO groups and controls calculated from the whole-blood viscosity values at the mean PCV.

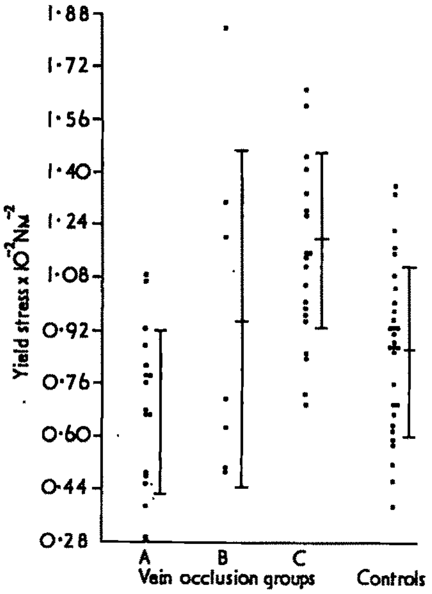

FIG. 5 *Yield stress values calculated at PCV at presentation for RVO and control groups. The mean and one standard deviation are indicated* (P<0·001 *for difference between groups A and C*)

This shows that after eliminating the influence of PCV on whole-blood viscosity and recalculating the yield stress RVO patients with capillary non-perfusion still had abnormal results. Taken as a whole, however, the RVO patients did not have yield stress values significantly higher than the control group.

Plasma viscosity results showed a highly significant difference (0·001<P<0·005) between the values of the two differently aged control groups. Comparing the RVO and older control group there was also significant difference (0·025<P<0·05), but between the RVO groups there was no difference. This analysis correlates well with the fibrinogen results below.

These results indicate that although the RVO patients had an abnormal plasma viscosity it was no higher in the patients with capillary non-perfusion than in those without.

HAEMATOLOGICAL RESULTS

Although there was no significant difference between the trapped plasma results in the RVO and control groups, analysis of the PCV result was done on the measured PCV after subtraction of the trapped plasma. Over all there was no significant difference between the control and total RVO groups ($0{\cdot}4 < P < 0{\cdot}5$). Further analysis allowing for variations of PCV between sexes did not alter the results. A highly significant difference, however, was found between groups A and C ($0{\cdot}001 < P < 0{\cdot}005$). Including group B with either A or C produced the same significance. Fig. 7 shows the PCV results of the RVO and control groups.

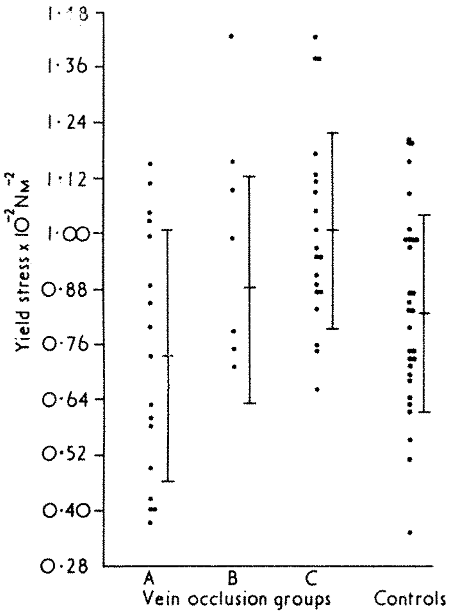

FIG. 6 *Yield stress values calculated after regression of viscosity results to a mean PCV of* 0·42. *Mean and one standard deviation are indicated* ($P < 0{\cdot}001$ *for difference between groups A and C*)

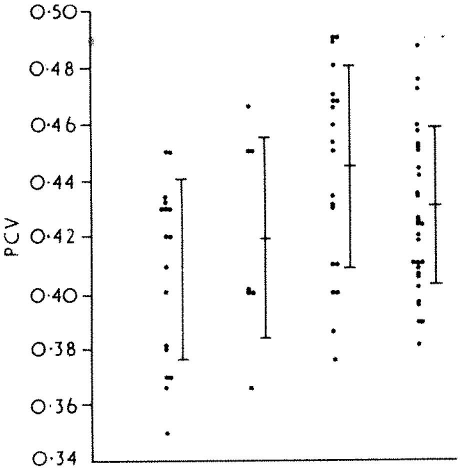

FIG. 7 *PCV values within RVO and control groups. Mean and one standard deviation are indicated* ($0{\cdot}001 < P < 0{\cdot}005$ *for difference between groups A and C*)

These findings show that patients with capillary non-perfusion had a higher PCV than those without non-perfusion.

The plasma fibrinogen levels showed a highly significant difference between the younger and older control groups ($0{\cdot}001 < P < 0{\cdot}005$). Because of the important influence of fibrinogen on viscosity the younger group was not included in the statistical analysis. Comparison of the older controls with the RVO group also showed a significant difference ($P < 0{\cdot}001$). There was no significant difference between the three RVO groups. Fig. 8 shows the relationship of the fibrinogen values.

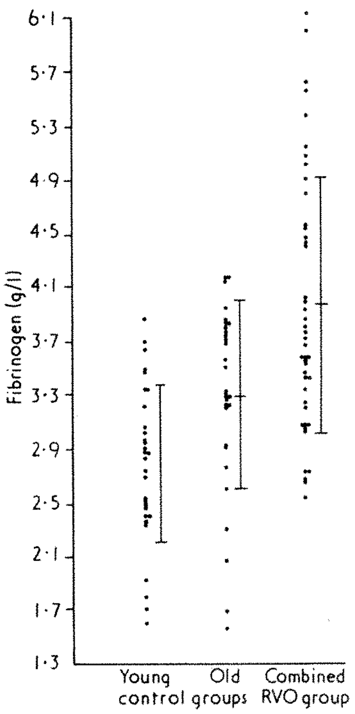

FIG. 8 *Plasma fibrinogen values in control RVO groups. Mean age of young and old control groups was* 30·7 *and* 57·9 *years respectively. Mean and one standard deviation are indicated*

These results indicate that plasma fibrinogen levels were abnormal in the RVO patients but the abnormality did not correlate with the presence or absence of capillary non-perfusion.

Other routine haematological investigations were normal in all control and patient groups, and in particular there were no patients or control subjects with a raised erythrocyte sedimentation rate. Blood films showed no evidence of any haematological disorder.

Table III *Summary of further investigations in the RVO and control groups*

Mean (±1 SD) of results

Investigation	*SI units*		*Traditional units*		*Significance*
	RVO group	*Controls*	*RVO group*	*Controls*	
Plasma viscosity	1·297 (0·07) $\times 10^{-3}$Nsm^{-2}	1·263 (0·04) $\times 10^{-}$N^{3}sm^{-2}	1·297 (0·07) cps	1·263 (0·04) cps	P < 0·05
Fibrinogen	3·98 (0·95) g/l	3·28 (0·69) g/l	397·8 (94·7) mg/100 ml	328·7 (69·4) mg/100 ml	P < 0·005
Uric acid	0·356 (0·087) mmol/l	0·321 (0·082) mmol/l	5·93 (1·36) mg/100 ml	5·35 (1·36) mg/100 ml	0·05 < P < 0·1
Creatinine	100·8 (27·4) mmol/l	91·9 (12·4) mmol/l	1·14 (0·31) mg/100 ml	1·04 (0·14) mg/100 ml	0·05 < P < 0·1
Total protein	72·6 (4·0) g/l	72·3 (3·0) g/l	7·26 (0·4) mg/100 ml	7·23 (0·3) mg/100 ml	NS
Immunoglobulins					
IgG	10·29 (1·99) g/l	10·25 (1·79) g/l	1029·6 (199·4) mg/100 ml	1025·3 (178·5) mg/100 ml	NS
IgA	2·35 (1·01) g/l	1·90 (0·64) g/l	234·6 (101·4) mg/100 ml	190·3 (63·8) mg/100 ml	P < 0·05
IgM	1·26 (0·62) g/l	1·21 (0·52) g/l	126·0 (62·0) mg/100 ml	121·4 (52·0) mg/100 ml	NS
Blood pressure					
Systolic	161·3 (30·1) mmHg	137·7 (12·6) mmHg	—	—	P < 0·001
Diastolic	94·1 (13·3) mmHg	87·3 (7·6) mmHg	—	—	P < 0·02
Trapped plasma	1·22 (0·07) per cent	1·21 (0·11) per cent	—	—	NS

NS = not significant

Table IV *Additional investigations in the RVO group*

Investigation	*No. investigated*	*Results*									
		SI units					*Traditional units*				
		Group mean	*Group A (±1 SD)*	*Group C (±1 SD)*	*Significance A–C*	*Laboratory range*	*Group mean*	*Group A (±1 SD)*	*Group C (±1 SD)*	*Significance A–C*	*Laboratory range*
Cholesterol	44	6·13 mmol/l	5·88 (1·33)	6·24 (1·15)	NS	2·59–6·22 mmol/l	236·4 mg/100 ml	226·8 (51·6)	241·0 (44·6)	NS	100–240 mg/100 ml
Fasting triglyceride	40	1·346 mmol/l	0·97 (0·35)	1·66 (0·64)	P < 0·001	0·68–1·81 mmol/l	119·1 mg/100 ml	85·7 (31·3)	147·4 (56·9)	P < 0·001	60–160 mg/100 ml
Complement C3	41	0·79 g/l				0·8–1·8 g/l	79·1 mg/100 ml				80–180 mg/100 ml
C4	10	0·35 g/l				0·2–0·8 g/l	34·6 mg/100 ml				20–50 mg/100 ml
Antinuclear	37	Negative									
factor	4	Positive 1:10									
	2	Positive 1:50									

NS = not significant

BIOCHEMICAL RESULTS

These are summarized in Table III. Serum uric acid levels were higher in the RVO group than the controls, and this became statistically significant when the control group was compared with group C ($0.01 < P < 0.02$). Serum creatinine, a more accurate indicator of renal function than urea values, was higher in the RVO group than in the controls although the difference was not statistically significant ($0.05 < P < 0.1$). Analysis of total serum proteins and serum globulins showed no significant differences between groups.

Immunoglobulin electrophoresis did not detect any dysproteinaemic state in the patients examined. IgG and IgM levels were not significantly different between the control and RVO groups but interestingly there was a significantly higher level of IgA in the RVO group ($0.025 < P < 0.05$).

Further investigations performed within the RVO group are summarized in Table IV, and show a high mean cholesterol level of 6·13 mmol/l (236·4 mg/100 ml) (range 3·76–8·94 mmol/l) (145–345 mg/100 ml). There were 24 patients with levels equal to or greater than our laboratory upper range of normal (6·22 mmol/l) (240 mg/100 ml).

Fasting triglycerides were estimated in only 40 RVO patients and 11 had levels equal to or greater than the upper limit of normal (1·81 mmol/l) (160 mg/100 ml). The mean level was 1·34 mmol/l (119 mg/100 ml) (range 0·45–2·66 mmol/l) (40–235 mg/100 ml).

C3 complement levels were equal to or less than the lower limit of normal (0·8 g/l; 80 mg/100 ml) in 22 patients (range 0·47–1·18 g/l; 47–118 mg/100 ml). C4 levels were measured in 10 of the patients with the lowest C3 levels but these were all normal. Antinuclear factor titres were all normal (< 1/10) except for equivocally raised levels in six patients (Table IV).

OTHER DISORDERS IN RVO GROUP

Blood pressure differences between the control and RVO groups showed a highly significant difference at systolic levels ($P < 0.001$) and a significant difference at diastolic levels ($0.01 < P < 0.02$). Eight patients were receiving treatment for hypertension at the time of diagnosis. Hypertensive treatment was started in nine patients after presentation. Four patients had received hypotensive therapy in the past but three of them were normotensive at presentation. Twenty-six patients (59% of the total group) were therefore considered to be normotensive. The total number of patients receiving or in need of hypotensive treatment was 18, and 14 of these had evidence of some capillary closure.

Glucose tolerance tests detected one diabetic in the group. Various forms of cardiovascular disease were present—intermittent claudication (one patient), history of deep vein thrombosis (three patients), myocardial infarct (one patient), and angina (one patient). One patient had had a bowel carcinoma resected three years previously.

Discussion

Before discussing our results we must comment on certain aspects of methodology.

PCV and hence whole-blood viscosity are influenced by venous stasis during collection of blood samples (Berry, Perkins, and Jernstrom, 1950) and by posture and mobility (Widdowson and McCance, 1950), and they are also subject to diurnal variation (Ehrly and Jung, 1973). Venous occlusion was therefore avoided and, so far as possible, all subjects were comparable in terms of posture and mobility when blood was taken. Ehrly and Jung (1973) emphasized the importance of sampling between 1 pm and 5 pm, when diurnal variations in factors affecting viscosity are most constant. We therefore used this period in our study.

Anticoagulation of the blood for viscosity measurement complied with the observation of Zingg, Sulev, and Morgan (1973), who found no difference in whole-blood viscosity in samples with heparin concentrations varying from 14–95 U/ml. Blood viscosity is critically temperature-dependent (Rand, Lacombe, Hunt, and Austin, 1964) and for this reason all measurements were done at a body temperature of 37°C.

The influence of age on PCV (Mayer, 1964) and fibrinogen (Ditzel and Kampmann, 1971) made it necessary to divide the 60 normal subjects into two groups, and 30 over the age of 45 years were used as a control group. Although the patient group and control group were not precisely matched for age, the mean age of 61·6 years of the RVO group compared closely with that of 57·9 years of the control group. The mean age in the RVO group collates well with other studies (Blankenship and Okun, 1973, 62·6 years; Michels and Gass, 1974, 63 years; Clemett, Kohner, and Hamilton, 1973, 59·5 years; Gutman and Zegarra, 1974, 57·5 years). There was no statistical difference between the mean ages of patients with and without capillary non-perfusion. However, they differed in PCV, whole-blood viscosity, and yield stress values. The ratio of men to women in the patient and control groups was about the same—namely, M:F 25:19 and 18:12 respectively.

Capillary viscometers with their inconstant shear rate have been used for many years to show differences in whole-blood viscosity. Wells, Denton, and

Merrill (1961) introduced a modification of a cone-plate viscometer to measure whole-blood viscosity. With the ability to control the shear rate interest has been focused on changes in blood constituents that might lead to an alteration in the rheological (flow) characteristics of blood. The question of whether increased blood viscosity is an aetiological factor in the development of thrombosis at sites other than the retinal circulation has been discussed by many authors. There is no doubt that retinal vein occlusion is a relatively common feature in conditions characterized by a hyperviscosity state—for example, polycythaemia (Duke-Elder, 1967) and macroglobulinaemia (Spalter, 1959). These conditions should obviously be sought in every patient developing a retinal vein occlusion or, of course, an occlusion at any other site. A hyperviscosity state, however, was not present in any of our patients. Some had raised immunoglobulin levels, but none high enough to cause hyperviscosity, and no patient had a PCV exceeding 0·50.

In this study higher levels of fibrinogen, plasma viscosity, and whole-blood viscosity, particularly at low shear rates, were found in the total patient group, especially in those with capillary non-perfusion, compared with the control group. The possibility that these abnormalities contribute to occlusion requires consideration. Ott and others (1974) found higher blood-viscosity values, more obviously significant at low shear rates, in patients with cerebral infarction compared to an age-matched control group. Blood viscosity measured at low shear rates was many times higher in patients suffering from arterial or venous thrombosis than in healthy individuals (Dintenfass, 1966). In a prospective study of postoperative venous thrombosis Dormandy and Edelman (1973) found a significant relationship between the development of thrombosis and raised blood viscosity and fibrinogen levels. They measured viscosity only at a shear rate of 230 s^{-1}, and probably a more striking difference would have been seen if they had measured viscosities at low shear rates. In veins the shear rate is lower than in other parts of the circulation (Whitmore, 1967; Dintenfass, 1971). Fibrinogen and the globulin fraction of blood are responsible for the formation of red cell aggregation (Chien, Usami, Dellenbach, and Gregerson, 1970), and it is this phenomenon that imparts the non-Newtonian behaviour of blood (Chien, Usami, Dellenbach, and Gregerson, 1967) with a rise in whole-blood viscosity at low shear rates.

The presence of a definite venous thrombosis in retinal vein occlusion has been questioned (Kohner and Shilling, 1976) and, indeed, the course of events still remains obscure. A consideration of the rheological events at the time of occlusion may add further insight into the pathophysiology of the condition. Fujino and others (1968) showed experimentally that complete venous occlusion produced arterial stagnation and an ischaemic retina, and that only partial occlusions produced a similar picture to that of CRVO. Furthermore, there is always evidence of some venous flow as shown by fluorescein angiography (Fujino and others, 1968; Oosterhuis, 1969). Similar clinical evidence supports the view that complete venous occlusion is only rarely observed in branch vein occlusion (Kohner and Shilling, 1976), although the damage to the vein wall and endothelial proliferation is an accepted pathological finding. The fact that a venous thrombosis partially occluding the lumen may occur but not lead to complete obstruction remains a possibility. A controlled randomized study of the role of a fibrinolytic agent, streptokinase, in CRVO concluded that it was not beneficial (Kohner, Hamilton, Bulpitt, and Dollery, 1974). This supports the suggestion that a venous thrombosis does not occur or, alternatively, that the introduction of streptokinase was too late after the occlusion for the patients to benefit from it.

Pathological changes in the vasculature of the retinal circulation are almost certainly a factor in the development of RVO. In BVO impedance of blood flow is virtually always at arterio-venous crossings (Gass, 1968) where there is either pressure on the vein or a thickened wall due to arterial disease or endothelial proliferation, or both. Similar pathological processes probably occur at the lamina cribrosa in CRVO but absolute confirmation is more difficult to obtain. Fluorescein angiography provides the proof of turbulence at arterio-venous crossings in BVO and on pathological grounds it is reasonable to expect a similar situation in CRVO.

Even when blood viscosity is normal a 'triggering mechanism' at the site of 'occlusion' might set off a rheological vicious circle, the decrease in flow (shear rate) causing an increase in blood viscosity owing to the non-Newtonian behaviour of blood. This would be followed by a further decrease in flow with a vicious circle type of increase in viscosity. Increase in viscosity has also been shown to occur with a reduction in pH (Murphy, 1967), and this might also occur locally after the initial period of slowing, further increasing viscosity. Rheological occlusion seems a possibility and this may or may not be followed by a true thrombosis. A 'rheologic obstruction' at the isometric phase of ventricular contraction, when the shear rate falls almost to zero, was suggested by Burch and De Pasquale (1965) as the cause of myocardial infarction in the absence of an anatomical obstruction of the coronary arteries. Retinal vein occlusion may be another example of 'rheological obstruction'. The triggering mechanism to the process is difficult to explain in terms of blood viscosity alone except perhaps in patients with much higher values. To study the possibility that higher blood-viscosity values predispose to the development of retinal vein 'occlusion' it would be necessary to do a prospective study on a group of patients with a similar degree of retinal vessel changes and without occlusion. Blood viscosity and the retinal appearances would need to be followed for a time. Finally, the group would be subdivided into those with and those without vein occlusion. Comparison of the viscosity values of the two groups would then give a clearer picture of the role of this factor.

The most striking finding in the present study was that of increased values for PCV and whole-blood viscosity in patients with capillary non-perfusion compared with those without. The precise mechanism of capillary non-perfusion remains obscure. Ashton (1970) mentions that in capillary non-perfusion the capillaries may not in fact be closed but that a state of circulatory stagnation may exist. This hypothesis seems very plausible in a situation where the viscosity of blood is increased. RVO patients have already been shown to have a higher viscosity than the control group, yet among these patients there is a group with even higher values. The fact that this is the group showing capillary non-perfusion suggests a close link with the theory of Ashton (1970). The vicious circle situation mentioned above might in the presence of higher viscosity predispose to a situation of circulatory stasis in some of the retinal capillary bed. The magnitude of the force required to re-establish flow (yield stress) in a stationary blood column would become critical, and it must be significant that this value is also higher in patients with non-perfusion than without. When capillary non-perfusion is present the distribution is usually patchy, and this probably represents local variation in shear stress and shear rate.

The importance of capillary non-perfusion has been investigated by Shilling and Kohner (1976). They found a statistically significant association between capillary non-perfusion and retinal neovascularization which is important in the morbidity of RVO due to vitreous haemorrhage, preretinal fibrosis, and retinal detachment. Hence patients with higher viscosity and yield stress values may well be at a greater risk of a more serious event with the development of capillary non-perfusion, retinal ischaemia, and its complications.

Our study shows therefore that differences in blood constituents may affect the outcome. This factor was considered in a study of acute myocardial infarction by Hershberg, Wells, and McGardy (1972), who found that there was no correlation between the PCV after admission to hospital and the eventual outcome of the episode. Viscosity values were not, however, measured, and Dormandy (1970) has commented that the PCV might not be a reasonable guide to the whole-blood viscosity value in a particular individual. Furthermore, acute myocardial infarction may be characterized by considerable systemic disturbance that might influence the value obtained for the PCV on a sample of blood taken after the infarction. Retinal vein occlusion is associated with no systemic disturbance.

Variation of PCV at different sites in the circulation is well recognized. The possibility arises that the PCV, and hence viscosity of a sample of blood taken from an antecubital vein, may not accurately reflect the PCV prevailing in the 'occluded' retinal vein. Therefore the dominant PCV influence on the whole-blood viscosity was eliminated and other factors influencing viscosity were analysed. This was done by the method of Dormandy (1970) where a log viscosity/PCV correlation equation was used to compare all results 'regressed' to the same mean PCV of 0·42. Significantly higher values were found for yield stress and whole-blood viscosity after carrying out this regression procedure when patients with capillary closure were compared to those without capillary closure.

There is general agreement that arterial vascular disease is commonly present in retinal vein occlusion (Braendstrup, 1950; Paton, Rubinstein, and Smith, 1964; Kohner, 1964; Raitta, 1965; Clements, Elsby, and Smith, 1968; McGrath and others, 1973; Gutman and Zegarra, 1974; Michels and Gass, 1974). This is supported by our observations that 41 per cent of the patients were receiving or required treatment for hypertension and that there were histories of angina (one patient), intermittent claudication (one patient), and myocardial infarction (one patient). Although analysis of the recorded blood pressures showed a statistical difference between the control and RVO groups it must be taken into account that the control group was selected to exclude hypertension. Comparison of recorded blood pressures between the RVO groups showed no statistical difference. The association of hypertension and capillary non-perfusion was also investigated using the χ^2 test. No significance between these two pathological changes could be found ($P = 0·118$) in our relatively small number of patients. A larger survery would probably decide whether there was any association.

Hyperlipidaemia is recognized as a factor in the development of arterial disease (Lewis, Chait, Wootton, Oakley, Krikler, Sigurdsson, February, Maurer, and Birkhead, 1974). Comparison between cholesterol levels in patients with and in those without large areas of capillary non-perfusion showed no difference, although the mean for the total group was only just within the upper limit for our laboratory (Table III). A significant difference ($P < 0.001$) was found in the fasting triglyceride levels comparing groups A and C. Hyperuricaemia has been linked with the development of arterial disease (Kannel, Dawber, Friedman, Glennon, and McNamara, 1964). Our total patient group compared with the controls had a higher serum uric acid. This does not reach statistical significance at the 5 per cent level but does so if group C is compared with the control group. In a group of patients with a high incidence of hypertension a relatively reduced level of renal function might be expected. Our patient group had a higher serum creatinine level than the controls, although this did not reach a statistically significant level ($0.05 < P < 0.1$).

These biochemical investigations support the strong association of arterial disease and retinal vein occlusion. They also suggest that the incidence of biochemical abnormalities is higher in those patients with capillary non-perfusion, which supports the recent observations of Shilling and Kohner (1976).

The absence in every patient of immunoglobulin changes compatible with a hyperviscosity syndrome has been commented upon. It is interesting, however, that a significantly higher IgA level was found between the control and the total patient group. The mean level of IgA in the retinal vein group, however, was not higher than the upper expected limit for our laboratory (4·0 g/l). McGrath and others (1973) found raised IgA levels in 14 of their 54 patients with retinal vein occlusion aged over 50 years. The actual levels found in their series were not mentioned. The finding of a higher IgA level in the retinal vein group remains unexplained.

Ellis, Hamer, Hunt, Lever, Lever, Peart, and Walker (1964) reported an association of neoplasia and systemic lupus erythematosis with retinal vascular occlusion. Our series does not show such a high incidence of neoplasia (only one patient) and ANF titres were all negative (< 1/10) except for equivocally raised levels in six patients (see Table III). Diabetes (Cohen, Staunton, Irving, and Gorchein, 1973) and glaucoma (Dryden, 1965) have been associated with retinal vein occlusion. Our finding of one patient with diabetes and two patients with raised intraocular pressure confirms the importance of seeking these conditions.

This study of blood and plasma viscosity has given a possible insight into the pathophysiology of the condition of retinal vein occlusion. The question of whether a therapeutic measure to alter the blood constituents could modify and moderate the morbidity of the condition is very difficult to assess. Possibly irreversible retinal damage, if it is going to occur, has already occurred before the patient presents. From a rheological stand point the only therapeutic measures available are venesection to lower the PCV, the use of an agent to lower the fibrinogen level, and treatment of hypertension if present. Clofibrate has been used by Dormandy, Gutteridge, Hoare, and Dormandy (1974) in patients with intermittent claudication and has been shown to lower both fibrinogen and whole-blood viscosity. Therapeutic phlebotomy has been shown by Burch and De Pasquale (1963) to benefit patients with angina pectoris, but they treated patients who had a PCV exceeding 0·50. This feature was not present in any of our patients.

Retinal vein occlusion may occur more than once in an individual. It would therefore seem reasonable that there should be a controlled study to determine whether such treatment reduces the incidence of further occlusion in patients with RVO who have a rheological abnormality which can be modified by treatment.

Summary

Whole-blood and plasma viscosity with haematological and biochemical investigations were measured in 44 patients with retinal vein occlusion. The patients were subdivided on the basis of fluorescein angiographic findings into:

1. Those with large areas of capillary non-perfusion.
2. Those with small areas of capillary non-perfusion.
3. Those with an intact capillary pattern.

Capillary non-perfusion in retinal vein occlusion is associated with a higher morbidity owing to the complications of retinal neovascularization. Significantly higher values of whole-blood viscosity, packed cell volume, and yield stress have been found in patients with capillary non-perfusion than in those without. These differences may be of critical importance during the episode of retinal vein occlusion and suggest an aetiological factor in the development of capillary non-perfusion. Higher whole-blood and plasma viscosity values and plasma fibrinogen levels have also been shown in the whole retinal vein occlusion group compared with a control group of 30 individuals. These differences may be a factor in the development of retinal vein occlusion but their precise role is difficult to evaluate.

Further biochemical investigations in the vein occlusion group supported the strong association with arterial disease and suggested a higher incidence of biochemical abnormalities in those patients with capillary non-perfusion.

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Fluorescein angiography and its prognostic significance in central retinal vein occlusion

L. LAATIKAINEN AND E. M. KOHNER
From the Retinal Diagnostic Unit, Moorfields Eye Hospital, London

There are three principal reactions of retinal blood vessels to veno-occlusive disease: dilatation of retinal veins and capillaries, abnormal vascular permeability, and vascular non-perfusion primarily affecting the capillaries. Fluorescein angiography permits localization and qualitative evaluation of abnormal vascular permeability (Gass, 1968). It shows clearly perfused capillaries and delineates areas of non-perfusion. The degree of capillary dilatation can be gauged by comparing the affected with the normal eye (dilatation of capillaries is usually associated with non-perfusion of others).

In order to determine the relevance of the various abnormalities observed on fluorescein angiograms in central retinal vein occlusion (CRVO) a prospective study was undertaken correlating the fluorescein angiographic findings with the final status of the eyes affected. The results are presented in this paper.

Patients and methods

Seventy-five eyes of consecutive patients with CRVO referred to the Retinal Diagnostic Department of Moorfields Eye Hospital or to Hammersmith Hospital were followed-up. Eyes with associated major retinal vascular disease like diabetic retinopathy were excluded. None of the patients received any specific treatment for the occlusion for at least one year after presentation. Symptomatic treatment for complications such as thrombotic glaucoma was given as required. The initial examination was done within one month of the first visual symptom in 60 cases (in 37 during the first week) and during the second and third months in 15 cases. After the initial presentation most patients were studied at three, six, and 12 months after the onset of symptoms. Some of those presenting during the first month had additional studies performed at six to eight weeks. At each visit a full eye examination and retinal photography were performed.

For fluorescein photographs 5 ml of 20 per cent sodium fluorescein was injected as fast as possible using either an antecubital intravenous injection or an intravenous catheter which was carried from the antecubital vein to the subclavian vein in order to get the best possible dye bolus in the retina.

ANGIOGRAPHIC FEATURES RECORDED

The following features were recorded in each fluorescein angiogram.

1. *Presence, absence, localization, and extent of retinal non-perfusion.* In retinal capillary non-perfusion central and peripheral areas of capillary closure were separated and the extent of non-perfusion was graded qualitatively as 0, +, or ++.
2. *Completeness of perifoveal capillary arcade.* The perifoveal capillary arcade was regarded as broken when a definite gap in its continuity was seen. In some cases it was impossible to assess the arcade fully in the first angiogram because of macular oedema or haemorrhage. In these eyes the intactness of the arcade was analysed later. Eyes in which no normal macular capillaries were present were recorded as a separate group.
3. *Presence or absence of fluorescein leakage in the macular area and source of such leakage.* Eyes with fluorescein leakage from postcapillary venules only but no obvious leakage from the perifoveal capillaries were separated from those with capillary leakage.
4. *Qualitative estimation of leakage from main veins.* Leakage from the main veins and the larger venous branches was graded as 0, +, ++, or +++. The amount of venous dilatation was not measured or arbitrarily estimated.
5. *Length of macular transit time.* This was defined as the time between the first fluorescein appearance in the main retinal arteries and its appearance in the macular veins. In most healthy eyes the fluorescein appears in the macular veins within 1–2 seconds of reaching the arteries. Therefore macular transit time of less than 2 seconds was regarded as 'normal' and 2 seconds or longer as 'delayed'.
6. *Disc or retinal new vessel formation.*

Arm to retina fluorescein circulation time was not compared with that of the normal eye because of inaccuracies due to variables in technical and circulatory factors.

CLINICAL GROUPINGS

The eyes were subdivided into the following five groups according to the one-year (final) visual acuity (VA),

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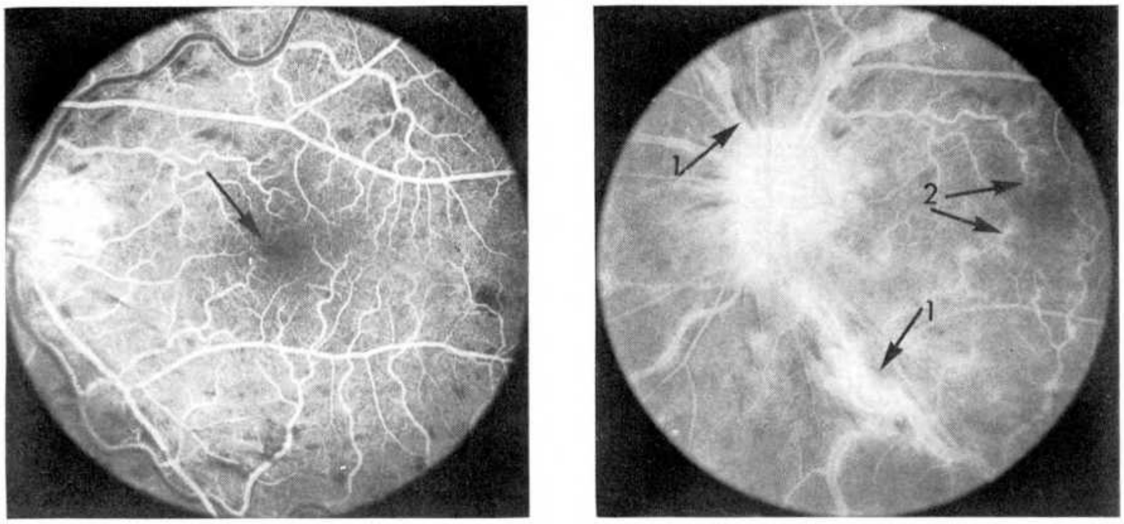
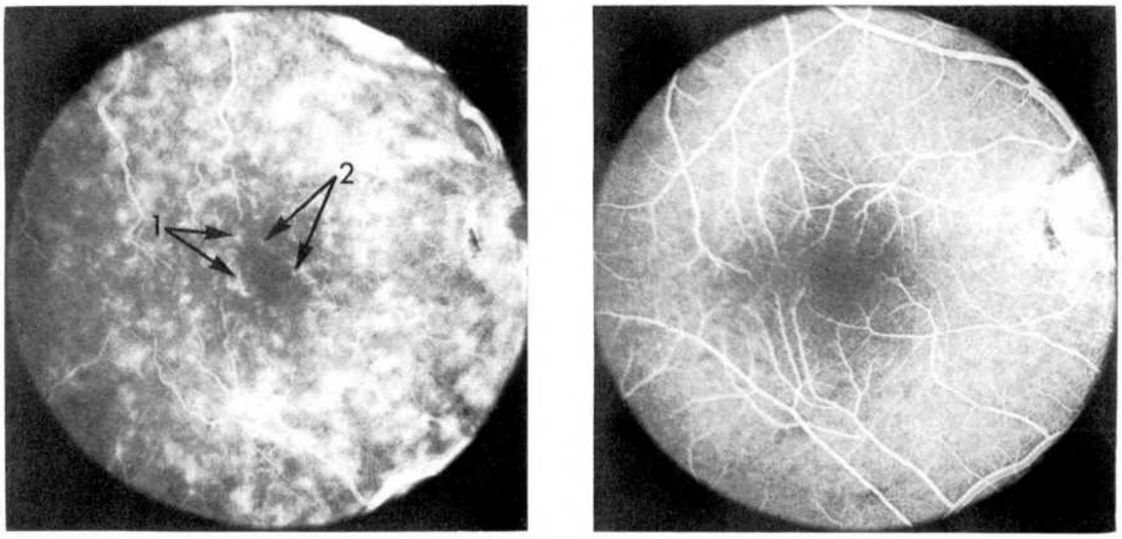
Address for reprints: Dr E. M. Kohner, Retinal Diagnostic Unit, Moorfields Eye Hospital, London EC1



(1*a*) (1*b*)

FIG. 1 *Mild CRVO.* (a) *Perifoveal capillary arcade nearly intact (arrow).* (b) *Same eye, late venous phase. Some leakage from main veins (arrows* 1) *and macular venules (arrows* 2) *but no obvious leakage from perifoveal capillaries*



(2*a*) (2*b*)

FIG. 2 *CRVO in acute stage.* (a) *Both venules (arrow* 1) *and capillaries (arrow* 2) *leak fluorescein.* (b) *Same as Fig.* 2a, 1 *year later. Complete resolution without leakage*

ophthalmoscopic changes, and complications. (1) Full resolution (VA 6/9 or better). (2) Partial resolution (VA 6/12—6/18) with or without ophthalmoscopically visible late changes. (3) Maculopathy (VA 6/24 or less due to chronic macular oedema or pigment epithelial changes and foveal scarring). (4) Thrombotic glaucoma. (5) Other major complications such as proliferating retinopathy, vitreous haemorrhage, retinal detachment (and preretinal fibrosis).

Results

FULL RESOLUTION

In 15 of the 16 eyes with good final VA the initial fluorescein angiogram showed good retinal capillary perfusion. In one eye some small areas of non-perfusion were seen in the periphery (Table I). The perifoveal capillary arcade was intact or near intact

Table I *Correlation between final outcome and retinal capillary non-perfusion (initial examination)*

Final outcome	*No. of eyes*	*Capillary non-perfusion*					
		None	*C−/P+*	*C+/P−*	*C+/P+*	*C++/P++*	*Not known*
Full resolution	16	15	1	–	–	–	–
Partial resolution	12	12	–	–	–	–	–
Maculopathy	24	11	–	7	6	–	–
Thrombotic glaucoma	13	2	–	–	3	7	1
Other complications	10	1	–	1	1	7	–
Total	75	41	1	8	10	14	1

C = Central areas of non-perfusion; P = Peripheral areas of non-perfusion; + = Small areas; + + = Extensive areas

Table II *Correlation between final outcome and completeness of perifoveal capillary arcade (initial study)*

Final outcome	*No. of eyes*	*Perifoveal arcade*			
		Intact	*Broken*	*No capillaries*	*Not known*
Full resolution	16	16	–	–	–
Partial resolution	12	11	1	–	–
Maculopathy	24	11	12	–	1
Thrombotic glaucoma	13	2	1	8	2
Other complications	10	–	2	7	1
Total	75	40	16	15	4

Table III *Correlation between final outcome and macular leakage (initial study)*

Final outcome	*No. of eyes*	*Macular leakage*		
		None	*Venular only*	*Capillary*
Full resolution	16	11	4	1
Partial resolution	12	4	4	4
Maculopathy	24	1	1	22
Thrombotic glaucoma	13	–	10*	3
Other complications	10	–	8*	2
Total	75	16	27	32

*From remaining veins (no or only few capillaries perfused)

in all eyes (Table II) and in 11 out of 16 no leakage from the macular vessels was seen. The macular venules leaked fluorescein in five (Fig. 1*a*, *b*), and in one of these there was also some capillary leakage (Table III). Macular transit time was normal in nine eyes and delayed in seven; in two the delay was more than 5 seconds (Table IV). Mild and localized leakage from the major veins was seen in eight of these eyes.

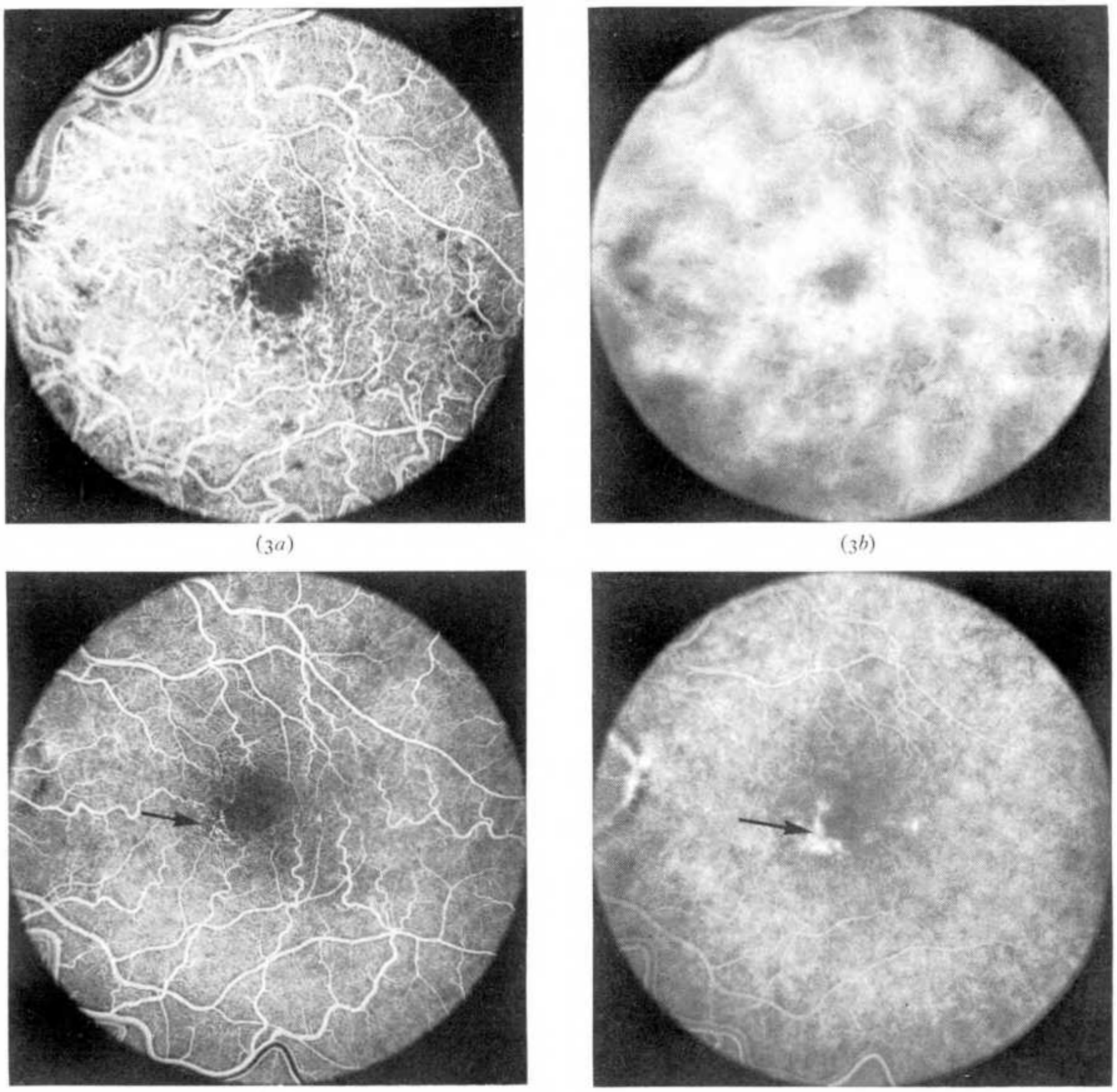
PARTIAL RESOLUTION

In 12 eyes a final VA of 6/12 to 6/18 was achieved. The fluorescein angiographic findings in this group did not differ significantly from those in the previous group. Capillary perfusion was good in all cases (Table I) and the perifoveal capillary arcade was intact in all but one eye (Table II). However, in this group leakage from the macular vessels was more common despite the intact arcade. Venous leakage was found in four eyes and in four there was combined macular capillary and venous leakage (Fig. 2*a*, *b*). Leakage from the larger veins was more common and more pronounced than in the previous group (Table IV). Macular transit time was normal in eight eyes, delayed in two eyes, and in two eyes it could not be measured (Table IV).

Table IV *Correlation between final outcome and macular transit time (seconds) and venous leakage (initial study)*

Final outcome	*No. of eyes*	*Macular transit time*			*Venous leakage*				
		<2s	*>2s*	*Not known*	*None*	+	+ +	+ + +	*Not known*
Full resolution	16	9	7	–	8	7	1	–	–
Partial resolution	12	8	2	2	4	4	2	2	–
Maculopathy	24	8	12	4	1	12	6	3	2
Thrombotic glaucoma	13	1	12	–	1	4	6	2	–
Other complications	10	–	10	–	–	2	6	2	–
Total	75	26	43	6	14	29	21	9	2

+ = Mild; + + = Moderate; + + + = Severe leakage



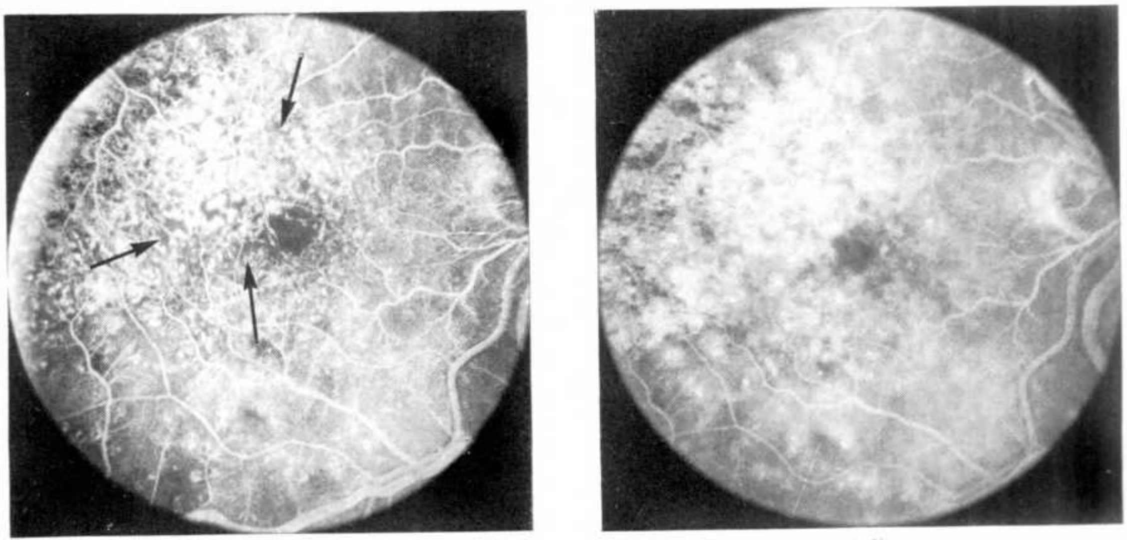
(3*a*) (3*b*)

(3*c*) (3*d*)

FIG. 3 *CRVO of moderate severity in acute stage.* (a) *Early venous phase; perifoveal arcade broken.* (b) *Same angiogram as* (a), *late venous phase. Diffuse leakage from perifoveal capillaries and venules.* (c) *Same as* (a) *after resolution. Small area of non-perfused and dilated capillaries outside the fovea* (*arrow*). (d) *Same angiogram as* (c), *late venous phase. Mild leakage from dilated capillaries* (*arrow*)

MACULOPATHY GROUP

In 11 of the 24 eyes in this group retinal capillary perfusion was good; no areas of non-perfusion were seen either in the centre or in the periphery (Fig. 3*a*, *b*, *c*, *d*). However in 13 eyes small areas of capillary closure were discovered at the posterior pole (Fig. 4*a*, *b*, *c*) and in six of them smaller peripheral non-perfused areas were also present (Table I). The perifoveal capillary arcade was intact in 11 eyes, broken in 12, and could not be seen in one (Table II). Leakage from macular capillaries was seen in 22 eyes, whereas the venules leaked in only one, and in one eye there was no leakage (Table III). Leakage from the main veins was a regular finding but in half the cases the venous leakage was very mild. Macular transit time was normal in eight eyes, delayed in 12 (in four it was 5 seconds or more), and could not be measured in four (Table IV).



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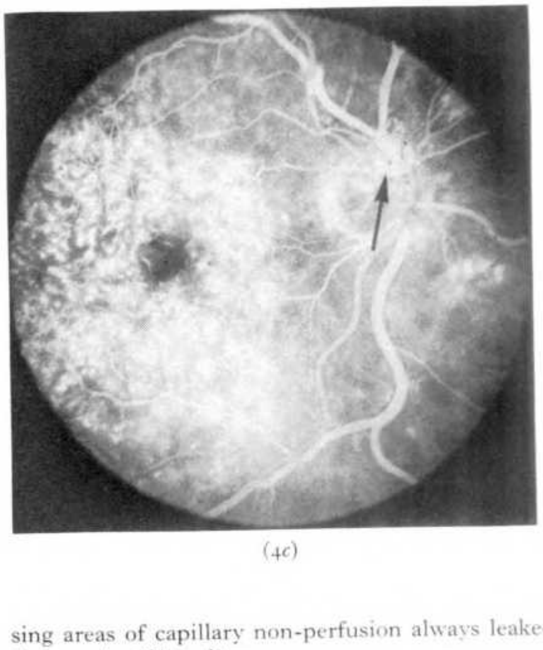


(4*c*)

FIG. 4 *CRVO of moderate severity 3 months after initial symptoms.* (a) *Perifoveal arcade broken, multiple small areas of capillary closure associated with dilated capillaries* (*arrows*). (b) *Same angiogram as* (a), *late venous phase. Extensive fluorescein leakage from dilated capillaries.* (c) *Same as* (b) *but 1 year later. More leakage in inferior nasal half of macula. Big retinociliary by-pass channel on disc* (*arrow*)

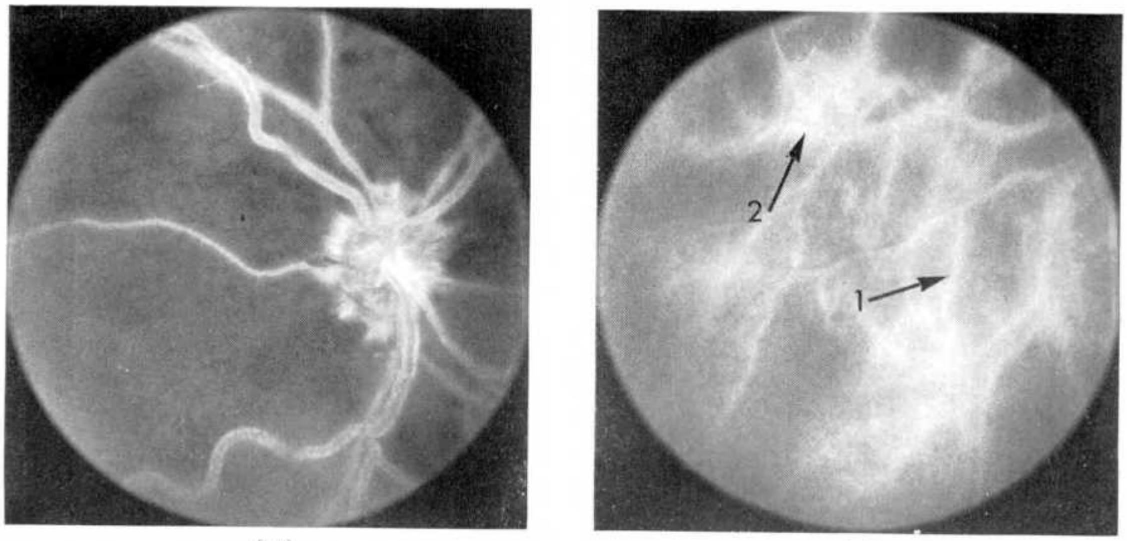
THROMBOTIC GLAUCOMA

At the initial presentation central and peripheral capillary non-perfusion was almost complete in seven (Fig. 5*a*, *b*) of the 13 eyes in this group, and capillary non-perfusion was less but still extensive in a further three. In one eye the retinal details could not be seen. By contrast, the remaining two eyes had good capillary perfusion at the time of the initial study (Table I) but extensive non-perfusion developed during the first three months. Most eyes showed increasing capillary and small vessel closure compared with the acute stage (Fig. 6*a*, *b*). As a result, at the three-month examination there was extensive central and peripheral non-perfusion in 10 of the 13 eyes, considerable non-perfusion in one, and in two corneal oedema made further photography impossible.

In one of the two eyes in which capillary perfusion was initially good the perifoveal capillary arcade was also intact in the first angiogram but there was capillary leakage. In one eye the perifoveal arcade was broken, and in two eyes it could not be seen (Table II). Eight of 13 eyes had no or only a few macular capillaries remaining. Large vessels crossing areas of capillary non-perfusion always leaked fluorescein (Fig. 5*b*).

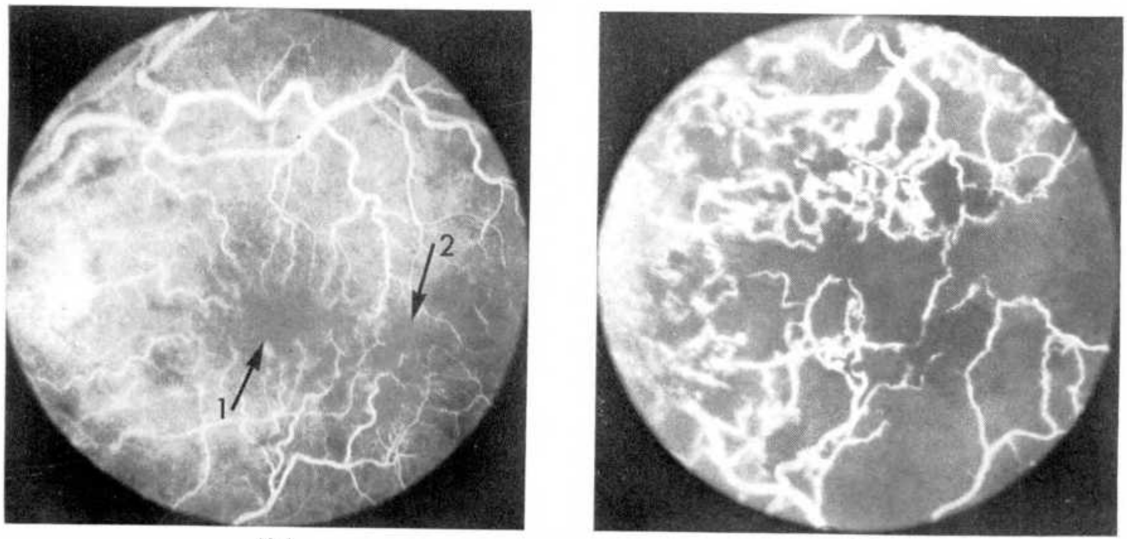
OTHER COMPLICATIONS

Proliferating retinopathy was present in seven eyes and preretinal fibrosis in three. The findings in these eyes are discussed together because the subgroups are small and the fluorescein appearance similar. All except one eye, which developed preretinal fibrosis, had poor capillary perfusion (Table I); in seven of the 10 eyes the central and peripheral capillary closure was extensive (Fig. 7*a*, *b*). The perifoveal capillary arcade was broken in two,



(5*a*) (5*b*)

FIG. 5 *Severe CRVO 7 weeks after first symptoms.* (a) *Complete capillary and small vessel closure at posterior pole.* (b) *Same angiogram as* (a), *inferior temporal periphery. Almost complete capillary closure, but arterioles* (*arrow* 1) *and venules* (*arrow* 2) *perfused. All vessels leak fluorescein*



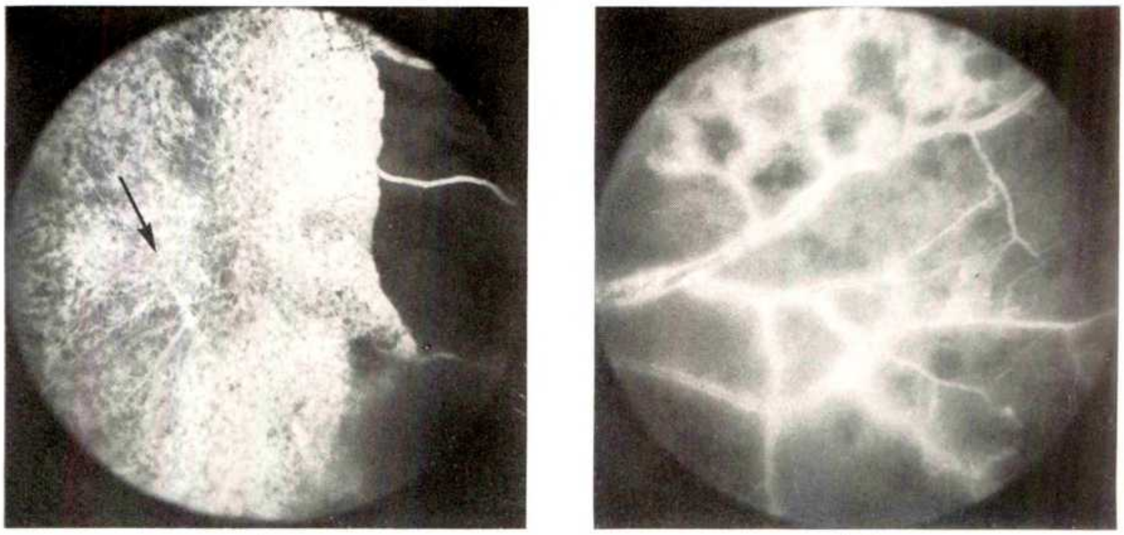
(6*a*) (6*b*)

FIG. 6 *CRVO in acute stage.* (a) *Perifoveal arcade broken* (*arrow* 1), *only small areas of capillary closure temporal to fovea* (*arrow* 2). (b) *Same as* (a) *one month later. Almost complete capillary closure throughout retina*

in seven no or only a few macular capillaries were left, and in one eye the capillary details could not be assessed (Table II). All major blood vessels crossing non-perfused areas leaked fluorescein. Macular transit time was delayed in all cases and in half of them it was 5 seconds or more (Table IV). All these patients had a final visual acuity of less than 6/60, and in five cases fluorescein angiography became impossible because of dense vitreous haemorrhage.

FINAL OUTCOME

The relationship between the final outcome and the extent and location of the capillary closure in the whole series of 75 eyes as it was seen at the three-month examination is shown in Fig. 8.



(7*a*) (7*b*)

FIG. 7 (a) *Severe CRVO with extensive new vessels (arrow marks centre of disc) 3 months after initial symptoms. Complete capillary closure in retina.* (b) *Same angiogram as* (a), *superior temporal periphery. Almost total capillary closure, remaining vessels leak fluorescein*

It seems from these studies that out of 75 eyes with CRVO just over one-third (28) had a visual acuity of 6/12 or better after one year. These patients all had good capillary perfusion and a near intact perifoveal capillary arcade in all but one patient. The macular transit time however was variable, as was the venous leakage.

Just under one-third (23) of the eyes became blind. Thrombotic glaucoma was the commonest cause. Large areas of central and peripheral non-perfusion were the hallmark in these eyes: in many no perifoveal capillaries were perfused. Leakage from veins also was more extensive and macular transit time often prolonged.

In the remaining 24 patients macular oedema and leakage from perifoveal capillaries predominated, as it did when they first presented.

Discussion

Previous studies of retinal branch vein occlusion have shown that the visual prognosis in eyes with an intact perifoveal capillary arcade is significantly better than in eyes with a broken arcade (Clemett, Kohner, and Hamilton, 1973). The present study shows that this also applies in CRVO; full resolution was seen only in eyes with an intact or nearly intact arcade. However, owing to permanently dilated and leaking capillaries, persistent cystoid macular oedema occurred in some, despite an intact arcade.

Fluorescein leakage from the retinal vessels indicates endothelial cell damage. In retinal vein occlusion this is due to increased intravenous pressure and to ischaemia of the vessel wall. In the mildest cases of CRVO only the terminal venules, the site of maximal increase in intravascular pressure, leak fluorescein and there may be minimal leakage from the main veins where they bend. Probably this leakage results from raised intraluminal pressure and not ischaemia. Leakage from the retinal capillaries is an indication of more extensive damage and a less favourable prognosis. Although a few eyes with macular capillary leakage resolved, some maculopathy or permanent macular oedema was the common outcome.

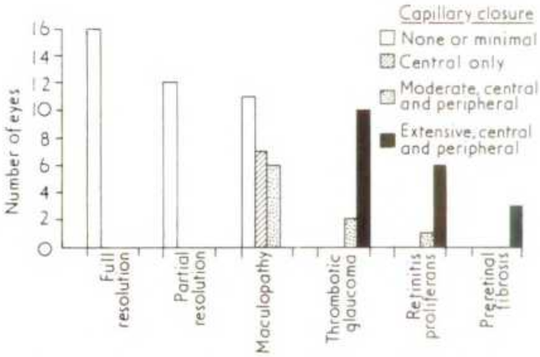


FIG. 8 *Histogram showing relationship between final outcome and retinal capillary closure at 3-month examination in 75 eyes with CRVO*

The mechanism of capillary closure in RVO is not known. Experimental work (Hockley, Tripathi, Ashton, Kohner, Hamilton, Bird, and Rosen, in press) shows that soon after occlusion some of the vessels are narrowed (although not occluded) presumably by extracellular oedema, while others may be occluded as the result of stagnation thrombosis. Retinal capillary closure is common in all vascular retinopathies such as diabetic retinopathy, sickle-cell retinopathy, and Eales's syndrome. In all these conditions large areas of non-perfusion have been associated with new vessel formation at the disc and the retina.

In diabetes and in CRVO neovascularization of the angle followed by thrombotic glaucoma is also common. This is never seen in diabetes unless there are large areas of peripheral non-perfusion. In preliminary studies of over 600 cases of diabetic retinopathy seen at the Hammersmith Hospital there were only four with rubeosis in the absence of neovascularization (Grindle, 1976). Thrombotic glaucoma developed during the first three to four months in CRVO and new vessels of the disc and retina were not a prominent feature in these cases, probably because they take many months to develop. This poor correlation between iris and retinal neovascularization in CRVO has already been noted by Smith (1955). The stimulus for new vessel formation, both in the retina and the iris, has been thought to come from the ischaemic retina (Wise, 1956; Ashton, 1961; Smith, 1961; Kohner, Shilling, and Hamilton, 1976). The findings in this study support this theory, because both thrombotic glaucoma and retinal and disc vessels developed only in those with *large* areas of both central and peripheral non-perfusion. Indeed, it was impossible to predict from fluorescein angiograms which of these complications was most likely.

Hill (1968) reported a correlation between 'mean retinal transit time' and venous dilatation in retinal vein occlusion. In this study macular transit time did not prove to be a valuable prognostic feature. While all patients with large non-perfused areas (and a poor prognosis) had some—often pronounced—slowing of the transit time, seven eyes with slow perfusion showed complete and two partial resolution. Leakage from arteries and veins and venous dilatation were unimportant findings compared with the site and extent of the capillary non-perfusion and the state of the perifoveal arcade.

In some of our cases the initial clinical and fluorescein angiographic picture of mild venous occlusion changed during the first three months to extensive capillary closure with poor visual prognosis. This shows that a visual prognosis within one month of presentation may be given only to those patients who have large non-perfused areas and in whom, therefore, the prognosis is poor. At three months an accurate prognosis can be given to all patients from the fluorescein appearances.

Summary

To determine the prognostic value of fluorescein angiograms in central retinal occlusion 75 patients presenting within the first three months of their initial visual symptoms were studied prospectively. The prognosis was found to be best (complete or partial resolution) in eyes with good capillary perfusion, an intact perifoveal capillary arcade, and leakage only from terminal venules and veins. A broken perifoveal capillary arcade and much capillary leakage, even in the absence of obvious capillary closure, were precursors of permanent macular oedema. All eyes with extensive capillary closure developed severe complications such as thrombotic glaucoma and neovascularization (preretinal fibrosis), and all became blind. Macular transit time and leakage from arteries and veins were not used as prognostic features.

Fluorescein angiography during the first month of the initial visual symptoms was of prognostic value only in those cases with poor prognosis. The three-month angiogram was an accurate indicator of the visual outcome in all cases.

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Cilio-retinal infarction after retinal vein occlusion

D. McLEOD AND C. P. RING*
From Moorfields Eye Hospital, London

Cilio-retinal arterioles are branches of the posterior ciliary arteries which supply areas of inner retina contiguous with the optic disc in about 20 per cent of individuals (Hayreh, 1963a). The cilio-retinal territory is spared from ischaemic necrosis after occlusion of the central retinal artery, while infarction of retina supplied by cilio-retinal arterioles may accompany ischaemic swelling of the disc when the posterior ciliary arteries are occluded in temporal arteritis (Hayreh, 1969).

Only two cases of retinal infarction in the cilio-retinal distribution have so far been described in association with occlusion of the central retinal vein (Oosterhuis, 1968; Hayreh, 1971), although such cases are not rare. The purpose of this paper is to present a series of 10 further cases together with a case of cilio-retinal infarction associated with a hemisphere branch retinal vein occlusion. The interrelationships between retinal vein occlusion and impaired posterior ciliary perfusion are discussed in the light of our findings.

Patients and methods

The 11 patients were drawn from the ophthalmic practice in Moorfields Eye Hospital (MEH), St Thomas's Hospital (STH), the Edinburgh Royal Infirmary (ERI), and the National Hospital, Queen Square (NHQS) (Table). Six patients were observed personally by one or other of us, while in the remaining cases we referred to case records and photographs. Fluorescein angiography was performed by the routine technique of the department concerned, in which 10 or 20 per cent fluorescein solution was injected into an antecubital vein. Photographs were generally taken at intervals of one second during the initial dye transit, using a Zeiss (Oberkochen) fundus camera. In all cases the initial photographic assessment was carried out within two weeks of the onset of symptoms and in seven cases within three days of visual loss. A medical examination and systemic investigation were carried out in most patients but were not standardized. Similarly, visual fields were tested by a variety of routine clinical techniques.

Results

CENTRAL RETINAL VEIN OCCLUSION (Cases 1–10)

The patients noticed sudden visual deterioration in one eye, and several complained specifically of a

Table *Particulars of 11 cases of cilio-retinal infarction*

Case no.	*Fig. no.*	*Source*	*Age (years)*	*Sex*	*No. of cilio-retinal arterioles*	*Eye*	*Visual acuity*		*Systemic disease*	*Blood pressure (mmHg)*
							At onset	*At one year*		
1	1	STH	35	Male	3	Left	6/60	6/4	—	120/90
2	2	MEH	79	Female	1	Right	CF	PL	Cerebrovascular insufficiency	190/100
3	3	MEH	41	Female	2	Right	6/24	6/6	Migraine	140/80
4	4	MEH	69	Male	1	Left	CF	CF	—	120/70
5	*	STH	50	Male	2	Right	6/60	6/12	Angina pectoris	110/70
6	†	ERI	52	Female	4	Right	6/18	6/4	—	110/70
7	‡	MEH	75	Female	2	Right	6/24	PL	—	160/90
8		MEH	32	Male	2	Left	6/18	6/9	—	110/90
9		MEH	69	Female	2	Right	CF	CF	Hypertension (on treatment)	170/100
10		NHQS	69	Female	3	Right	6/60	6/18	Arteriosclerosis	130/80
11	5	MEH	39	Female	2	Left	6/18	6/12	—	150/90

*Fig. 4 in McLeod (1975b); †Fig. 1 in McLeod (1975a); ‡Fig. 6 in McLeod (1976)
CF = counting fingers; PL = perception of light

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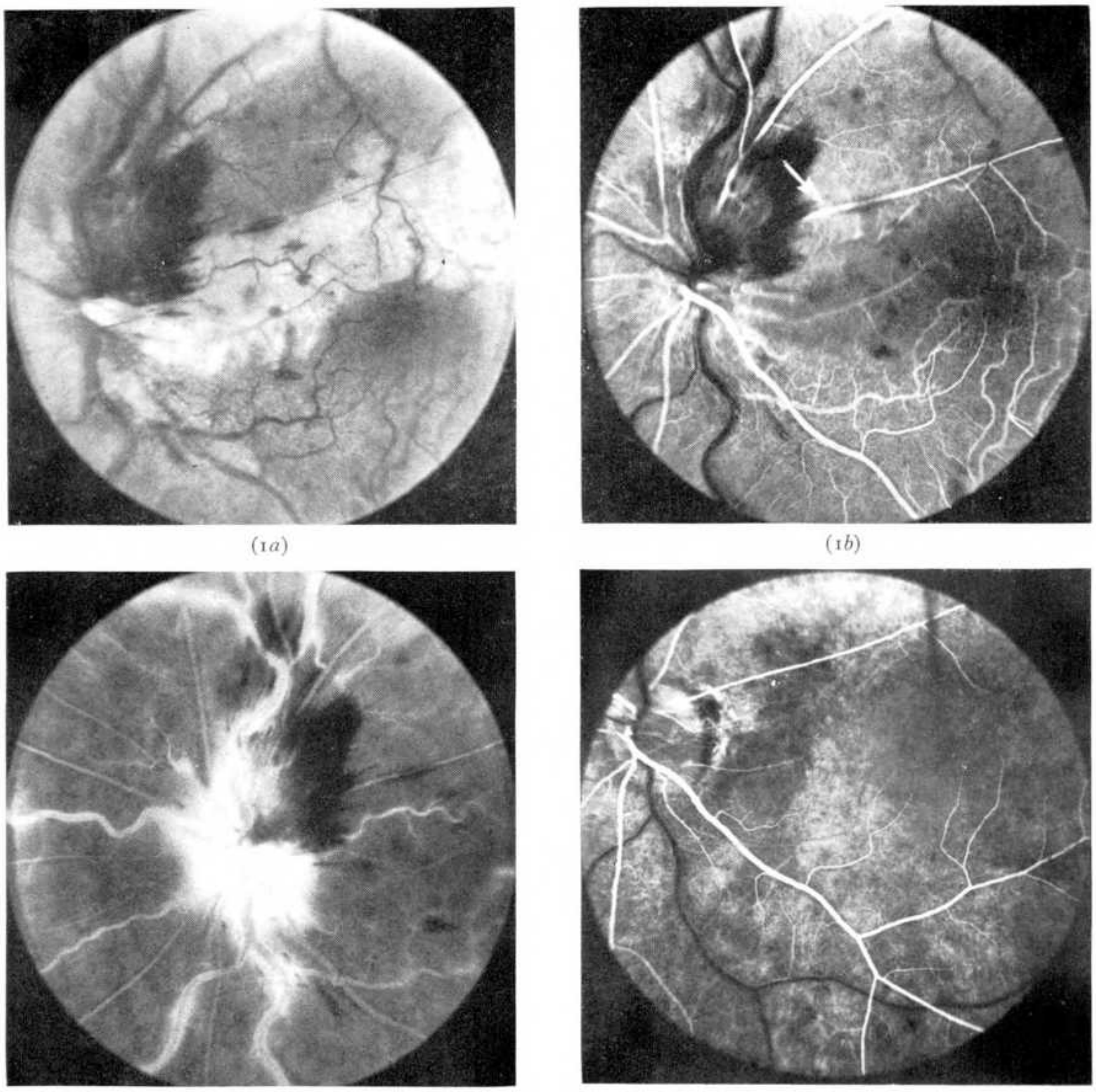
Address for reprints: D. McLeod, FRCS, Moorfields Eye Hospital, City Road, London EC1V 2PD


(1*a*) (1*b*)

(1*c*) (1*d*)

FIG. 1 *Case* 1. (a) *Fundus photograph* 10 *days after visual loss: retinal infarction in cilio-retinal territories.* (b) *Fluorescein angiogram (same study as* (a)): *early arterio-venous phase, larger cilio-retinal arteriole (arrow) has filled.* (c) *Fluorescein angiogram (same study as* (a)): *late phase, dye leakage from disc and veins.* (d) *Fluorescein angiogram seven months later: early arterio-venous phase, delayed peripapillary choroidal filling*

localized scotoma in the central field of vision. Pre-existing ocular lesions had been discovered in only one patient (case 2), who was known to have had bilateral preretinal macular fibrosis for six years.

Anterior segment

On presentation there was no significant abnormality in the anterior segment or ocular media of any patient; in particular, there were no inflammatory signs in the aqueous or anterior vitreous. Apart from a single patient with mild chronic glaucoma (case 9), the intraocular pressure was normal in each eye, though the pressure in the affected eye was generally 2–4 mmHg less than that in its fellow.

Presenting fundus signs

Funduscopy showed widespread retinal haemorrhages (including blot haemorrhages anterior to the equator) together with distension and tortuosity of all tributaries of the central retinal vein (Fig. 1). Some patients showed occasional perivenous cotton-wool spots or retinal oedema, especially at the macula.

In addition to signs of central vein occlusion, retinal pallor was seen contiguous with the optic disc, and parts of the periphery of these areas showed an intense whiteness. The clinical appearance was that of ischaemic cloudy swelling of the inner retina. The infarcts comprised the territories of supply of cilio-retinal arterioles, and in the eight patients with multiple cilio-retinal vessels each cilio-retinal territory was infarcted. Haemorrhages were present within the infarcts but were generally few in number, except in case 2 (Fig. 2).

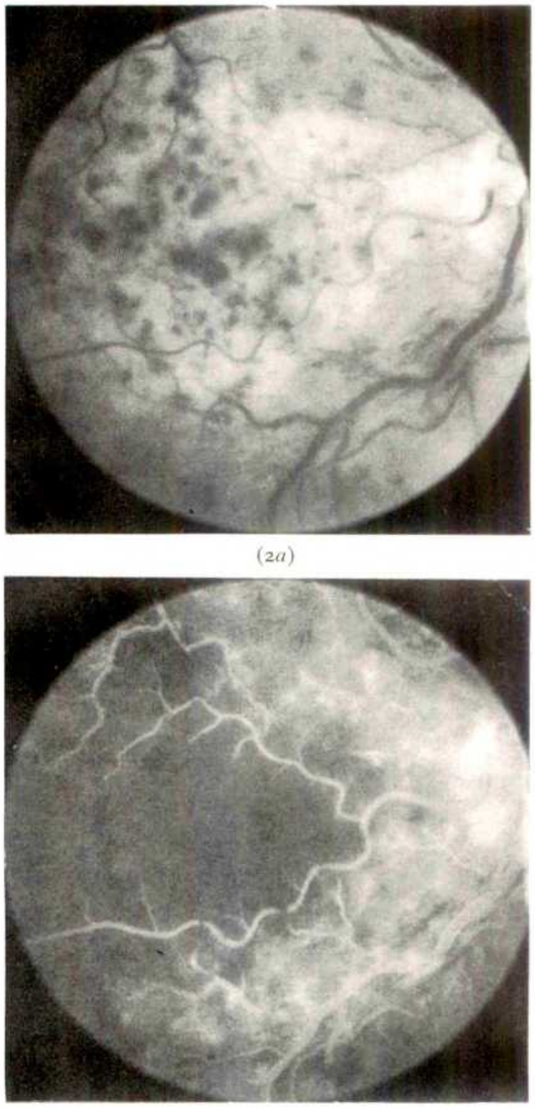
There was variable swelling of the optic nerve head on presentation (Figs 1, 3), and marked disc pallor was observed in case 7 and in the lower half of the disc in case 4 (Fig. 4). Papillary haemorrhages were conspicuous in some cases, but absent in others (Figs 1, 3).

Fluorescein angiography

The intraretinal circulation time (from dye appearance in the central artery to filling of the major veins at the optic disc) exceeded eight seconds in all cases. The central retinal capillary bed was engorged and fluorescein often leaked from venules or larger veins in the late phases (Figs 1, 2).

Fluorescein perfusion through the cilio-retinal circulation was consistently impaired relative to central arterial perfusion, and the arrival of fluorescein in cilio-retinal arterioles was never observed to precede the arrival of dye in the central artery. The cilio-retinal vessels contained dye in the first available frame of the central arterial transit in seven cases, while cilio-retinal arteriolar filling was delayed in cases 6, 9, and 10. In four patients (cases 1, 5, 6, and 8) an intact, engorged cilio-retinal microcirculation was demonstrated with occasional knob-like capillary dilatations resembling microaneurysms. In the remaining six cases the advancement of dye along the cilio-retinal arterioles was very slow, and reversal of flow (Fig. 3*c*) was seen in cases 2, 3, 7, and 9. The lack of capillary pattern and dye leakage clearly distinguished the cilio-retinal territory from the central retinal supply (Fig. 2) and venules crossing the infarct filled with dye from the adjacent circulation. Retrograde entry of dye into the cilio-retinal capillary bed was sometimes seen in these cases (Fig. 3*c*).

Angiographic assessment of the posterior ciliary circulation to the optic disc was often difficult because of haemorrhage, but delayed filling of the disc microcirculation was sometimes demonstrable (Fig. 3). There was variable late leakage of dye from the optic disc (Figs 1, 3).

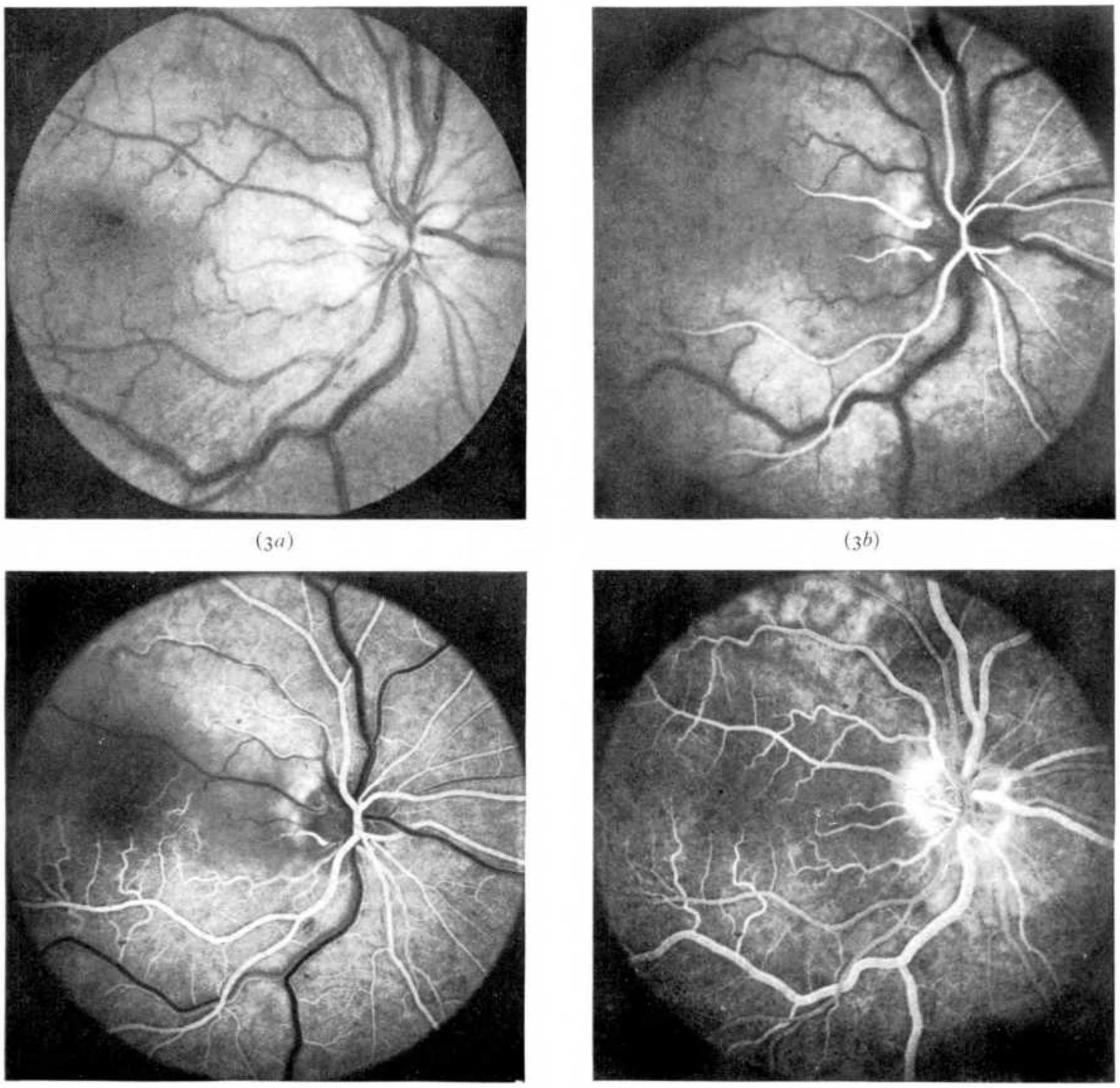

(2*a*)

(2*b*)

FIG. 2 *Case* 2. (a) *Fundus photograph three days after visual loss: haemorrhagic cilio-retinal infarct.* (b) *Fluorescein angiogram: late phase, dye leakage from venules in central arterial territory*

Visual function

The presenting visual acuities in the affected eyes are shown in the Table. Although cloudy retinal swelling involved the papillo-macular bundle in all cases, central fixation was preserved except in case 2,



(3*a*) (3*b*) (3*c*) (3*d*)

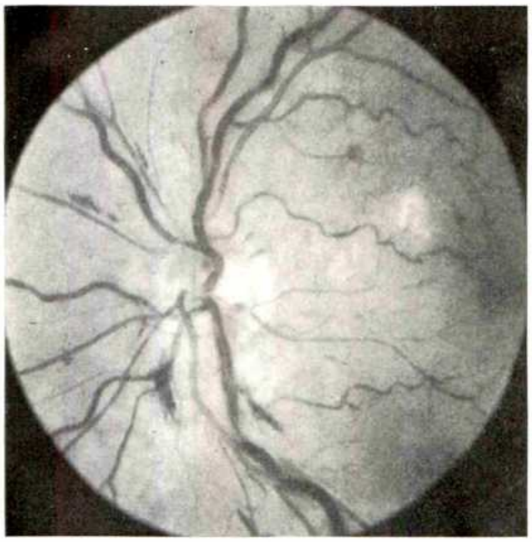
FIG. 3 *Case* 3. (a) *Fundus photograph one day after visual loss: mild ischaemic disc swelling, cilio-retinal infarcts and venous distension.* (b) *Fluorescein angiogram: retinal arterial phase, truncated dye front in cilio-retinal arterioles.* (c) *Fluorescein angiogram: early arterio-venous phase, reversal of flow in cilio-retinal arterioles, optic disc not filled.* (d) *Fluorescein angiogram: late phase, minimal disc-leakage*

in which a large cilio-retinal arteriole supplied most of the posterior retina (Fig. 2).

Visual field examination revealed absolute scotomata which extended from the blind spot and corresponded with the distribution of retinal infarction. The scotoma split fixation in cases 1, 3, 4, 5, and 7 because the cilio-retinal supply contributed to the perifoveal capillary arcade. In addition to these absolute defects, field loss in the remaining visual field reflected retinal oedema and haemorrhage or optic nerve head ischaemia. An extensive upper field defect in case 4, for example, resulted from infarction of the lower half of the optic disc.

General medical examination

Systemic disorders found in the patients and possibly significant in the aetiology of their ocular vascular occlusions are shown in the Table. There was no evidence of temporal arteritis in any patient.



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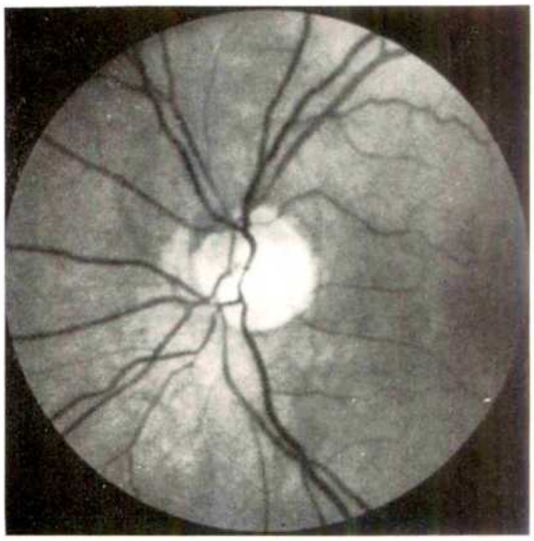

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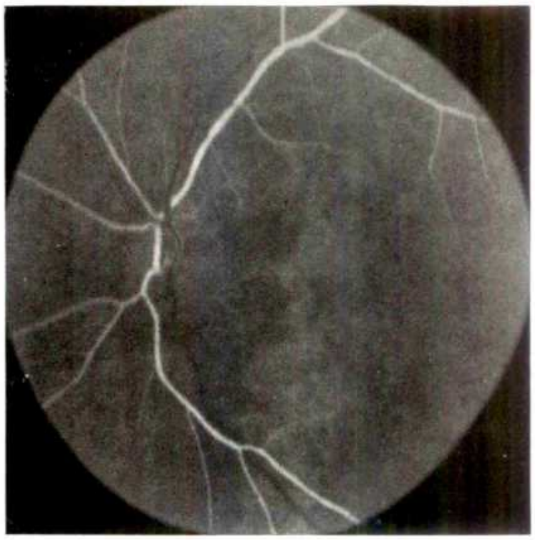


(4*c*)

FIG. 4 *Case* 4. (a) *Fundus photograph three days after visual loss: accumulations of axoplasmic debris in retina (two cotton-wool spots) and inferonasally on disc.* (b) *Fundus photograph five months later: optic atrophy except superonasally.* (c) *Fluorescein angiogram (same study as* (b)): *retinal arterial phase, delayed filling of disc vessels, peripapillary choroid, and cilio-retinal arteriole*

Course

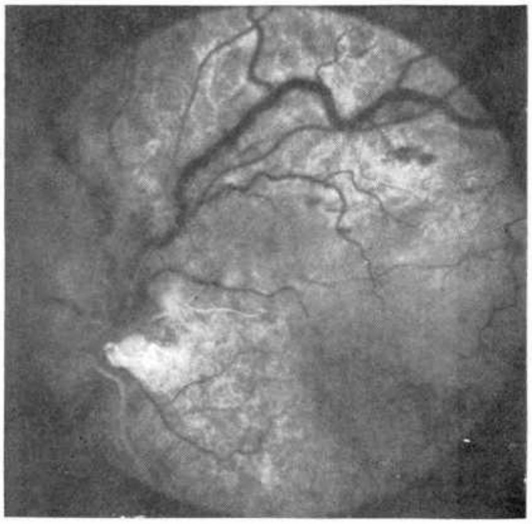
Rubeotic glaucoma developed within three months of presentation in two patients (cases 2 and 7). In the remaining eight cases venous distension subsided within a few weeks, with absorption of retinal haemorrhages and oedema. Visible retinociliary venous bypass channels developed in five patients (cases 1, 3, 5, 6, and 10) and six patients showed some improvement in central vision (Table). The optic disc swelling subsided and localized sectors of pallor of the disc reflected ascending optic atrophy secondary to cilio-retinal infarction; atrophy and cupping of the lower half of the disc was seen in case 4 (Fig. 4).

Although no unequivocal angiographic evidence of impaired choroidal perfusion had been found on presentation, retinal haemorrhages and oedema made the initial assessment difficult and delayed peripapillary choroidal filling was demonstrated in cases 1, 4, 5, and 6 on follow-up (Figs 1, 4).

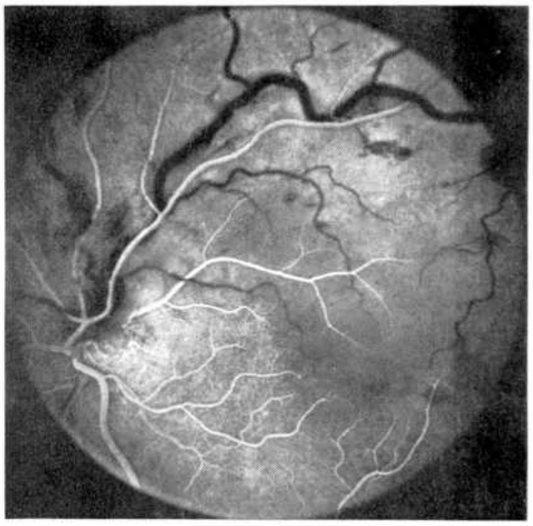
HEMISPHERE BRANCH RETINAL VEIN OCCLUSION
(Case 11)

A 39-year-old woman noticed sudden blurring of vision in her left eye the day before presentation. Funduscopy showed distension and tortuosity of the veins draining the superior retinal hemisphere. The upper rim of the optic disc was swollen and cloudy retinal swelling was seen in the superior macular area. The retinal infarct consisted of that part of the cilio-retinal circulation which drained into the obstructed vein (Fig. 5). Fluorescein angiography revealed extremely slow perfusion of a dilated capillary bed within the ischaemic area. However, the cilio-retinal territories drained by the inferotemporal branch vein filled satisfactorily with dye and showed no cloudy swelling or related field defect.

Signs of venous obstruction subsided within a



(5*a*)



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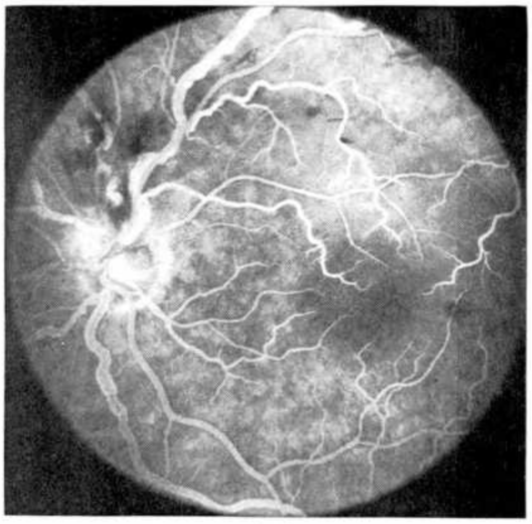

(5*c*)

FIG. 5 *Case* 11. *Fluorescein angiograms one day after visual loss.* (a) *Preretinal arterial phase, masking of choroidal fluorescence by retinal oedema, lower branch of upper cilio-retinal arteriole has filled.* (b) *Retinal arterial phase in drainage area of superior hemisphere vein, retinal venous phase in drainage area of inferior hemisphere vein.* (c) *Late phase, dilated capillaries in ischaemic area, slight disc leakage.*

few weeks without treatment and left no sequelae apart from a permanent scotoma below fixation, localized retinal atrophy, and slight sectoral disc pallor.

Discussion

CLINICAL PICTURE

The patients in this series presented a varied clinical picture typical of acute retinal vein occlusion. Several cases conformed to the description of venous obstruction in youth and middle age designated 'retinal vasculitis' by Lyle and Wybar (1961), 'papillophlebitis' by Lonn and Hoyt (1966), and 'optic disc vasculitis' by Hayreh (1972). These patients illustrated the characteristic tolerance of a young microcirculation to raised intraluminal pressure and showed a tendency for spontaneous recovery without treatment, which has been attributed to the facility for developing retino-ciliary bypass channels (Hart, Sanders, and Miller, 1971). However, rubeotic glaucoma, a frequent complication of central vein occlusion, developed in two elderly patients in the series.

Retinal pallor, corresponding absolute visual field defects, and grossly retarded perfusion by fluorescein provided unequivocal clinical proof of ischaemic cloudy swelling in the cilio-retinal territories. This was also suggested by the signs of accumulated axoplasmic debris at the periphery of the infarcts (McLeod, 1975a) and the subsequent localized inner retinal atrophy with loss of superficial reflexes from nerve-fibre bundles. However, the ischaemic retina in these cases differed in certain respects from infarcts due to 'pure' arteriolar occlusion. Haemorrhages, for example, were present within the cilio-retinal territories and were extensive in a patient who had pre-existing disease of the macular capillary bed (case 2, Fig. 2). In addition the cilio-retinal circulation was demonstrably engorged in some cases and capillary dilatations resembling microaneurysms were also seen.

In no case of central vein occlusion have we observed retinal infarction localized to the territory of a branch of the central retinal artery, so this complication appears to be a development peculiar to the cilio-retinal circulation. This must reflect the independent origin of cilio-retinal arterioles from the posterior ciliary vessels. However, relatively few patients with cilio-retinal arterioles who suffer a central vein obstruction develop retinal infarction in the cilio-retinal territories (McLeod, 1975b). The two groups of patients (that is, those with and those without cilio-retinal infarction) cannot be distinguished either by the severity of venous obstruction or by the size of their cilio-retinal vessels.

CIRCULATORY PHYSIOLOGY

The intraluminal pressure in the major ocular veins (P_v) normally approximates to the intraocular pressure (P_{io}), probably owing to changes in cross-sectional diameter of these vessels as they leave the globe—a vascular waterfall (Permutt and Riley, 1963). The perfusion pressure (PP) driving blood through the capillary circulations of the retina, choroid, and optic nerve head is therefore defined as the mean arterial blood pressure (P_a) minus the intraocular pressure (P_{io})—that is, $PP = P_a - P_{io}$.

A reduction in blood flow thus follows obstruction of the central retinal or posterior ciliary arteries, though the effects on perfusion may be counteracted by autoregulatory changes in the calibre of precapillary resistance vessels which tend to maintain blood flow despite changes in perfusion pressure (Alm and Bill, 1972). Ischaemic changes occur in the inner retina, outer retina, or optic nerve head when, despite autoregulatory vasodilatation and collateral flow, capillary perfusion is insufficient to meet the individual metabolic requirements of the various ocular tissues.

Obstruction of the vortex or retinal veins also causes a reduction in blood flow ($PP = P_a - P_v$), while the increase in transmural pressure across small vessels is an important determinant of transudation and haemorrhage formation. Passive dilatation of capillaries and venules may reduce their flow-resistance after venous obstruction (Phillips, Brind, and Levy, 1955; Folkow, 1962), but the autoregulatory responses of precapillary arterioles after retinal vein occlusion have not been established. Increased transmural pressure gradients might be expected to result in arteriolar *constriction* due to a local myogenic reflex (Bayliss, 1902); alternatively, *vasodilatation* might be expected in response to retinal hypoxia and accumulation of metabolites after severe venous occlusion—'metabolic autoregulation'.

The increase in intraluminal pressure in the major retinal veins after central vein occlusion depends upon the change in venous outflow resistance and also upon the arterial blood pressure (since this determines the maximum venous pressure attainable). Total obstruction to retinal venous outflow has been achieved experimentally by neoprene latex occlusion of the central vein and potential retino-ciliary bypass channels (Fujino, Curtin, and Norton, 1969). The central venous pressure presumably approached the *systolic* arterial pressure in these animals and a haemorrhagic retinal infarct resulted. Central vein obstructions are seldom associated clinically with a complete failure of retinal perfusion. Hart and others (1971) have suggested that the central venous pressure approaches the *diastolic* arterial pressure, but Duke-Elder and Gloster (1968) emphasized that ophthalmodynamometry is unsuitable for assessing either arterial or venous pressures within the eye.

PATHOGENESIS OF CILIO-RETINAL INFARCTION

Symptoms and signs of venous obstruction and retinal ischaemia were recent in all our cases, suggesting that these events occurred simultaneously and probably interdependently. Furthermore, in case 11 retinal infarction developed only in that part of the cilio-retinal territory which was drained by the obstructed branch vein, indicating that retinal ischaemia was precipitated by venous occlusion.

We have assumed that the metabolic requirements of the inner retina were the same in the central retinal and cilio-retinal territories and that identical blood flowed through similar capillary beds. Furthermore, impaired cilio-retinal perfusion was considered the cause and not the result of retinal infarction. Given that the central retinal and cilio-retinal supplies both drain into the central retinal vein, the localized severe reduction in cilio-retinal perfusion must reflect either an increased resistance to blood flow along the cilio-retinal arterioles (compared with the central retinal arterioles) or a relatively low driving pressure in the posterior ciliary supply.

(*a*) *Increased resistance to flow*

Precapillary arterioles in the central retinal and cilio-retinal circulations may differ in their autoregulatory responses to venous occlusion. However, it is unlikely that retinal infarction resulted from a localized failure of metabolic autoregulation in the cilio-retinal circulation, and an exaggerated reflex constriction of cilio-retinal arterioles (Bayliss effect) is not in keeping with known autoregulatory responses in branches of the posterior ciliary vessels (Alm and Bill, 1972).

Alternatively, the selective severe impairment of cilio-retinal perfusion in these cases might reflect a relatively high 'vasomotor tone' in the posterior ciliary and cilio-retinal arteries, as postulated by Blumenthal, Best, Galin, and Gitter (1971). However, any conclusions drawn from ophthalmodynamoangiographic studies are open to question (Archer, Ernest, and Krill, 1972).

(*b*) *Reduction in input arterial pressure*

A lower driving pressure in the posterior ciliary arteries relative to that in the central artery could result in a localized failure of cilio-retinal perfusion after central vein occlusion. The cilio-retinal arterial pressure might approximate to a raised venous pressure sustained by the input pressure in the larger central arterial supply; the arterio-venous perfusion pressure gradient in the cilio-retinal circulation would thus be effectively eliminated.

Unfortunately, there is no satisfactory clinical method of quantifying or comparing input arterial pressures in the various ocular circulations (Duke-Elder and Gloster, 1968) and therefore no good evidence of whether the pressure in the posterior ciliary supply differs appreciably from that in the central retinal artery in normal individuals. The failure of cilio-retinal perfusion in our cases might reflect some anatomical variation—for example, an unusually distal origin of the ciliary supply from the ophthalmic artery, or an exceptionally long extraocular course or peculiar pattern of branching of the posterior ciliary vessels.

Alternatively, this clinical picture may result from central vein occlusion in patients who have a pre-existing asymptomatic obstruction to flow in the posterior ciliary circulation which is insufficient in itself to produce ischaemic changes in the outer retina, optic nerve head, or cilio-retinal territory. Such a partial arterial obstruction might reflect the presence of generalized vascular disease in patients who develop retinal vein occlusions. Simultaneous infarction of all cilio-retinal territories in patients with multiple cilio-retinal arterioles indicates that any localized obstruction to flow must have been situated proximal to the emergence of these vessels from the optic disc, and the peripapillary choroidal filling defects could be interpreted as indicating an associated reduction in choroidal blood flow. However, although the central retinal vein is the major efferent channel from the optic disc (Hayreh, 1963b; Anderson, 1970), symptoms of ischaemic disc-swelling were lacking in several of our cases, presumably owing to the utilization of alternative drainage pathways from the disc into choroidal or pial veins; dilatation of these channels is part of the process of retino-ciliary collateral formation (Hayreh, 1969). In this way isolated infarction of the cilio-retinal territories reflected the fact that the cilio-retinal circulation is the only part of the posterior ciliary supply that depends entirely on the central vein for drainage.

Conclusions

Central vein occlusion in patients with partial obstruction of their posterior ciliary arteries may be the explanation for at least some of our cases, though the relative contribution of reduced ciliary arterial pressure and raised venous pressure to cilio-retinal ischaemia probably varied from patient to patient. In some cases a critical reduction in cilio-retinal perfusion resulted from a degree of central vein obstruction that caused few exudative or haemorrhagic sequelae in the central retinal territory. Indeed, some patients might not have presented had they not possessed a cilio-retinal arterial supply, since central vein occlusion often produces minimal symptoms in the absence of macular oedema (Hart and others, 1971).

Although experimental central vein occlusion is known to cause severe retinal ischaemia (Fujino and others, 1969) the relationship between retinal infarction and venous occlusion is less clearly defined clinically. These cases show that under certain conditions venous occlusion may result in acute retinal infarction in the absence of significant haemorrhage or extracellular oedema.

This series may represent a spectrum of ocular vascular lesions intermediate between acute central retinal vein occlusion and acute ischaemic optic neuropathy (which is commonly associated with peripapillary haemorrhages and venous dilatation).

Summary

Retinal ischaemia in the territory supplied by cilio-retinal arterioles is described in 10 patients with signs of central retinal vein occlusion and in another patient with a hemisphere branch vein occlusion. The venous occlusion was transitory in nine of the 11 cases, but two elderly patients developed rubeotic glaucoma.

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Central retinal artery occlusion (reversible) in sickle trait with glaucoma

RONALD L. RADIUS AND DANIEL FINKELSTEIN
From the Wilmer Ophthalmological Institute, The Johns Hopkins University and Hospital, Baltimore, Maryland, USA

Retinal vascular occlusions of several types occur in the various sickle haemoglobin disorders (SS, SA, SC, S-Thal) (Edington and Sarkies, 1952; Henry and Chapman, 1954; Goldberg, 1971a; Kennedy and Cope, 1958; Isbey, Clifford, and Tanaka, 1958; Lieb, Geeraets, and Guerry, 1959). Occlusions are primarily of small vessels in the peripheral retina preceding the development of neovascularization (Welch and Goldberg, 1966; Goldberg, 1971a, b). Occlusions of small vessels in the macula have also been reported in SS and SC haemoglobinopathy (Knapp, 1972; Acacio and Goldberg, 1973; Ryan, 1974). They are probably due to intravascular emboli of sickled red blood cells (Welch and Goldberg, 1966; Goldberg, 1971a, b). Factors known to enhance sickling of red cells thereby influencing the risk of vascular thrombosis include hypoxia, dehydration, lowered pH, and hyperviscosity (Sherman, 1940; Griggs and Harris, 1956; Perillie and Epstein, 1962; Charache and Conley, 1964). Not surprisingly, therefore, under certain conditions occlusion of large vessels such as the central retinal artery occur (Kabakow, Van Wiemokly, and Lyons, 1955; Conrad and Penner, 1967; Stein and Gay, 1970; Michelson and Pfaffenbach, 1972). We report a case of central retinal artery occlusion in SA disease immediately after diuretic and hyperosmotic therapy for acute traumatic glaucoma. We believe that this treatment must be used cautiously in the sickle patient whose ocular circulation is already compromised by acute glaucoma.

Case report

An 18-year-old black woman presented to the Wilmer emergency room with a traumatic hyphaema 24 hours after a blunt ocular injury. Her medical and family history were unremarkable. Uncorrected visual acuity was light perception right eye, 20/20 left eye. The anterior chamber contained diffuse haemorrhage with a layered hyphaema of about 10 per cent. Ocular motility was normal. Intraocular pressure by applanation was 55 mmHg. The fundus could not be visualized through the anterior chamber blood. Examination of the left eye was normal in all respects.

Treatment consisted of atropine cycloplegia, topical dexamethasone, and 120 ml glycerol 75 per cent. Emesis followed shortly after osmotic therapy. Intraocular pressure remained raised at 55 mmHg. Subsequent treatment consisted of intravenous acetazolamide 500 mg and mannitol 100 g (1·5 g/kg) at an infusion rate of 5 g/minute. One hour later ocular tension was 55 mmHg. Vision in the right eye was no light perception when tested with the American optical indirect ophthalmoscope at maximum voltage.

The clinical impression was that the patient had suffered a central retinal artery occlusion. An anterior chamber paracentesis of 0·08 ml was performed. After this vision returned to brisk light perception. Intraocular pressure was subsequently controlled with oral acetazolamide. With clearing of the ocular haemorrhage fundus examination showed disc hyperaemia. Fluorescein angiography was essentially unremarkable. Electroretinography could not be performed. Subsequent serum electrophoresis showed sickle-cell trait (SA) haemoglobinopathy with 42 per cent sickle-cell haemoglobin. Visual acuity returned to the 20/30 level.

Discussion

Our patient presented with an intraocular pressure of 55 mmHg and brisk light perception vision. One hour after diuretic and osmotic therapy the pressure remained at 55 mmHg with no light perception. This time sequence suggests that increased intravascular tonicity and altered haemodynamics after these medications may have precipitated an occlusion in an already compromised vascular system. Intravenous infusion of mannitol is known to increase serum osmolarity from 10–40 mosm/l depending on rate of infusion and dosage (Galin, Davidson, and Pasmanik, 1963; Weiss and Wise, 1962; Kolker and Hetherington, 1970). Increased serum tonicity occurs rapidly throughout the infusion and returns to equilibrium

Address for reprints: D. Finkelstein, MD, The Wilmer Ophthalmological Institute, Johns Hopkins University and Hospital, Baltimore, Maryland 21205, USA

over a period of from one to two hours (Galin and others, 1963; Weiss and Wise, 1962). The effect of intravenous acetazolamide is difficult to quantify.

The susceptibility of patients with sickle-trait haemoglobinopathy to central retinal artery occlusion at moderately raised or even normal ocular pressures has been well documented. Five cases of central retinal artery occlusion have been reported (Kabakow and others, 1955; Conrad and Penner, 1967; Stein and Gay, 1970; Michelson and Pfaffenbach, 1972). Bilateral vascular occlusions were described in a 36-year-old patient with active pulmonary tuberculosis, systemic lupus erythematosus, and sickle-cell trait (Kabakow and others, 1955). Conrad and Penner described central retinal artery occlusion in a 32-year-old pilot with sickle-trait haemoglobinopathy (unassociated with active flying duties) (Conrad and Penner, 1967). No other precipitating ocular or systemic conditions were found; the proportion of sickle haemoglobin was 42 per cent. Vision remained at no light perception in the affected eye. Stein and Gay reported bilateral arterial occlusions in a six-month-old infant suffering from high fever and marked dehydration (Stein and Gay, 1970). They suggest that metabolic abnormalities induced by pneumonia and renal failure in this SA infant might well have produced intravascular sickling leading to bilateral central artery occlusion. Finally, Michelson and Pfaffenbach described two sickle-trait youths with arterial occlusions after blunt trauma and ocular haemorrhage (Michelson and Pfaffenbach, 1972). Both these patients were treated with diuretic and osmotic agents to control raised intraocular pressures ranging from 20 to 50 mmHg.

Various factors affect the severity of the symptoms in patients with sickle-cell disease. Percentage of abnormal haemoglobin as well as oxygen tension, lowered pH, fever, vascular stasis, hyperkalaemia, raised carbon dioxide level, and serum hypertonicity increase the amount of erythrocyte sickling and subsequent clinical symptoms (Sherman, 1940; Griggs and Harris, 1956; Perillie and Epstein, 1962; Charache and Conley, 1964). Increased serum tonicity after diuretic and osmotic medications in combination with vascular stasis, presumably coincident with raised intraocular pressures, may have precipitated vascular occlusion in this patient with sickle-cell trait.

The possibility that ocular hypotensive medications may have aggravated the situation calls for re-evaluation of the management of raised ocular tension in black patients. We recommend an emergency sickle cell preparation as part of the initial examination of every black patient with hyphaema. In those with sickle-cell haemoglobin an intraocular pressure over 40 mmHg requires careful monitoring of vision for the earliest sign of vascular occlusion. Osmotic agents should be given with caution and vision must be checked frequently thereafter. Only experience with similar cases will show whether such medications must always be avoided.

In our case good visual function returned after retinal blood flow had apparently ceased. Recent reports emphasize that retinal function may return even when vascular occlusion lasts up to one hour or more. Neuronal function may be much more resistant to absolute ischaemia than previously recognized. After reversible ligation of the central retinal artery in Squirrel monkeys Kroll (1968) showed that a period of retinal ischaemia limited to 15 minutes produced no significant gross or histological damage. Only after one hour of obstruction was the earliest neuronal damage seen. Reinecke, Kuwabara, Cogan, and Weis (1962) produced retinal ischaemia in cats by increasing intraocular pressure above systolic arterial pressure by external massage. In cases in which ischaemia was limited to less than 1½ hours only minimal histopathological changes were noted. Lessell and Miller (1975) produced total cerebral as well as retinal ischaemia by cross-clamping the ascending aorta in adult Rhesus monkeys. When the arterial obstruction was released after periods of 14 to 24 minutes 14 of the 22 monkeys had survived this vascular insult, and when periods of post-arrest hypotension were avoided, histopathological retinal abnormalities were not seen.

These histopathological studies have been corroborated by a number of experiments to assess the functional resistance of retinal tissue to ischaemia. After reversible occlusion of the retinal vascular supply in rabbits electroretinograms have returned to pre-insult levels when anoxia was limited to 10 minutes (Arden and Greaves, 1956). Popp (1955) found that even after 60 to 90 minutes of ischaemia partial recovery was seen in the rabbit ERG. Working with Squirrel monkeys, Hamasaki and Kroll (1968) produced reversible retinal artery occlusion by placing a ligature round the surgically exposed vessel. Remarkably, they showed that more than two hours of occlusion were required to produce irreversible changes in electrical activity of the retina and optic nerve. Gouras and Hoff (1970) made similar observations using an isolated, perfused mammalian eye system. Extending these studies to man, Wegner (1928) produced retinal ischaemia in pre-enucleation specimens by raising ocular tension well above systolic pressures. When the period of retinal ischaemia was limited to 15 minutes visual recovery was full: even after 45 minutes of ischaemia some function returned. Under similar experimental conditions Böck, Bornschein, and Hommer (1963, 1964) showed that complete recovery of both electrical and physiological retinal activity can be obtained even after so long as one hour of absolute retinal ischaemia. Such investigations suggest that moderate periods of ischaemia may be expected to show significant functional recovery if adequate blood supply is restored and maintained.

We emphasize that the sickle-cell patient with an intraocular pressure over 40 mmHg is approaching a precarious situation which may be exacerbated by osmotic therapy. In our case function returned from no light perception to 20/30 vision. A review of the literature on experimental occlusion suggests that efforts to restore vision even after one to two hours of known occlusion should not be considered only heroic.

Summary

We report a case of central retinal artery occlusion in an 18-year-old black woman with sickle-trait haemoglobinopathy and acute glaucoma after hyphaema. The central retinal artery occlusion occurred immediately after treatment of the glaucoma with osmotic agents, raising the possibility that they played a precipitating role. We suggest that osmotic agents be used with extreme caution in sickle patients with glaucoma. The occlusion was treated by anterior chamber paracentesis with eventual return of good vision. The reversibility of retinal and optic nerve function after total ischaemia is discussed.

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Macular and perimacular vascular remodelling in sickling haemoglobinopathies

G. K. ASDOURIAN, K. C. NAGPAL, B. BUSSE, M. GOLDBAUM,
D. PATRIANAKOS, M. F. RABB, AND M. F. GOLDBERG
From the Sickle Cell Eye Clinic, University of Illinois
Eye and Ear Infirmary, Chicago, Illinois

Peripheral retinal vascular changes in patients with sickling haemoglobinopathies (Welch and Goldberg, 1966; Goldberg, 1971a, b; Condon and Serjeant, 1972a, b, c) include both non-proliferative and proliferative lesions. Dynamic vascular remodelling of the peripheral vasculature of the retina has also been documented (Galinos, Asdourian, Woolf, Stevens, Lee, Goldberg, Chow, and Busse, 1975). Reports of posterior pole changes in patients with sickling haemoglobinopathies have described these changes as either acute, such as central retinal artery occlusion and macular arteriolar occlusions (Knapp, 1972; Acacio and Goldberg, 1973; Ryan, 1974), or as chronic manifestations of vascular occlusions, including microaneurysm-like dots, dark and enlarged segments of terminal arterioles, hairpin-shaped venular loops, and pathological avascular zones (Stevens, Busse, Lee, Woolf, Galinos, and Goldberg, 1974). Visual function may or may not be affected as a result of these vascular changes (Goldberg, 1973; Stevens and others, 1974).

This paper further documents these posterior pole changes and characterizes their evolution as determined prospectively over a long follow-up period.

Patients and methods

During the last three years the Sickle Cell Eye Clinic screened over 400 patients with sickling haemoglobinopathies. The purpose was to identify patients with early stages of proliferative retinopathy. Fluorescein angiography was performed whenever there was the least suspicion of retinopathy.

Since macular changes were found in some 20 per cent of the clinic's population (Stevens and others, 1974) more attention and careful evaluation have been given to the study of the posterior pole. Kodachrome photographs and fluorescein angiograms of the posterior pole were taken in all patients at four-month intervals. Fluorescein angiography was performed in the manner of Novotny and Alvis (1961) using a Zeiss Fundus-Flash III camera. Kodachrome II film was used for colour photography; angiograms were taken with Kodak Tri-X film processed in Kodak D-11 (1:1 dilution) for nine minutes at 70°F. Spectrotech exciter and barrier filters were used.

After the injection of fluorescein (10 per cent fluorescein sodium solution), through an indwelling paediatric scalp vein needle inserted near the patient's antecubital fossa, phase angiograms of the macular area were taken at the rate of one frame per second. The fine capillary network of the posterior pole was selectively focused. Repeat injections of small increments of 1 to 1·5 ml were given as needed to maintain a high degree of fluorescent contrast within the macular capillary network. Careful attention was also given to the region of the horizontal vascular 'raphe', which is similar in location to the horizontal nerve fibre raphe (Vrabec, 1966). Many vertically orientated arterioles appear to terminate along this vascular raphe.

Patients with posterior pole abnormalities were investigated for colour vision abnormalities and visual field changes. Pseudoisochromatic charts, the Farnsworth D-15 panel, Farnsworth-Munsell 100-hue test, and the Nagel anomaloscope were used in assessing colour vision. The tangent screen, Goldmann perimeter, and Amsler grid were used to detect visual field changes. More recently we used static perimetry to assess minute visual field abnormalities.

Results

One hundred consecutive patients with various haemoglobinopathies underwent selective fluorescein angiography of the macular area and the area of the temporal raphe. Altogether 41 of the patients had homozygous sickle-cell disease (HbSS), 36 had sickle cell-haemoglobin C disease (HbSC), 15 had sickle cell-thalassaemia disease (HbS-thal), seven had sickle cell trait (HbAS), and one had homozygous haemoglobin C disease (HbCC). A total of 29 patients had abnormalities of the macular area, the temporal raphe area, or both. Of the patients with abnormal maculae 13 (44·8 per cent) had HbSS, 13 (44·8 per cent) had HbSC,

Address for reprints: Dr M. F. Goldberg, University of Illinois Eye and Ear Infirmary, 1855 W Taylor Street, Chicago, Illinois 60612, USA

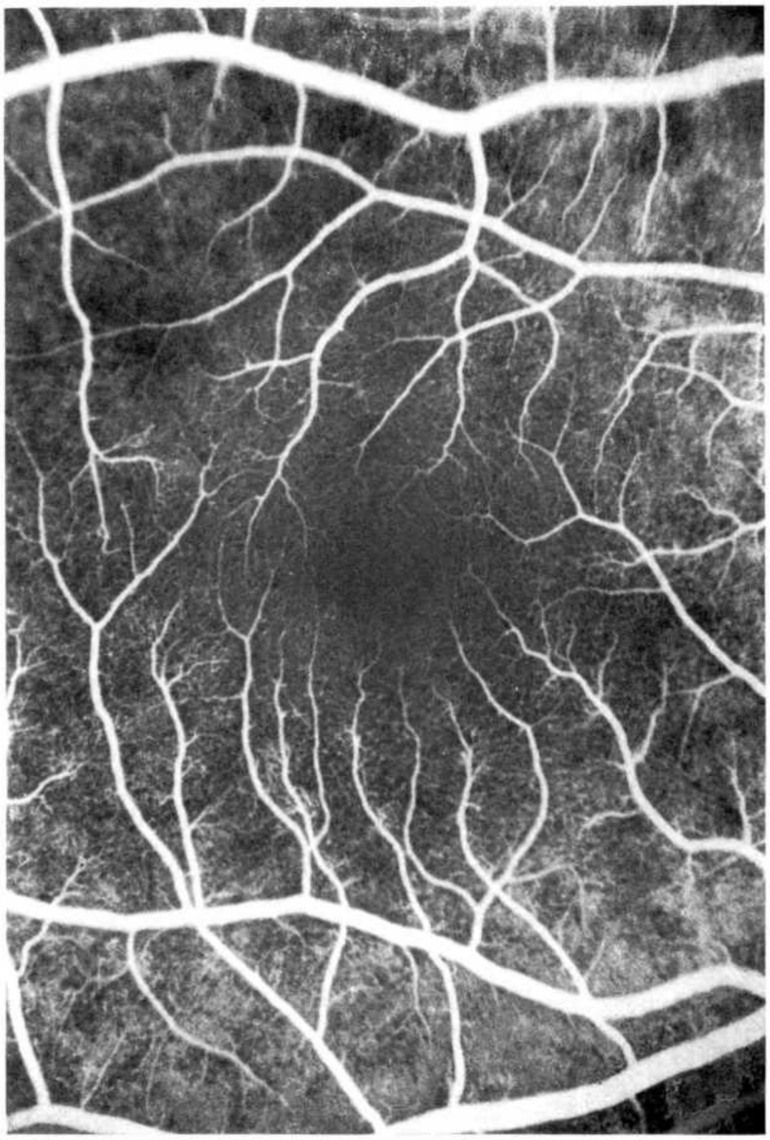


FIG. 1 *Case 1. Fluorescein angiogram of right eye before acute obstructive episode of normal macular vasculature*

and three (10·4 per cent) had HbS-thal. Of the patients with different haemoglobinopathies 31·7 per cent of HbSS, 36·1 per cent of HbSC, and 20 per cent of HbS-thal patients had abnormal maculae. All HbAS patients and the single HbCC patient had normal macular angiograms.

CASE REPORTS

Case 1

A 26-year-old Black woman with sickle cell-haemoglobin C disease (haemoglobin S 52 per cent; haemoglobin C 48 per cent) was admitted to the Eye and Ear Infirmary in February 1974 because of vitreous haemorrhage in the left eye. Eight months previously she had been found to have stage I retinopathy (peripheral arteriolar occlusions) (Goldberg, 1971b) in the left eye. On admission her general physical examination was normal. Blood pressure was 105/80 mmHg. Her fasting serum glucose level, oral glucose tolerance test, and serological tests for syphilis were normal.

Her visual acuity was 20/20 in the right eye and 20/70 in the left. Slit-lamp examination of the anterior segment revealed minimal conjunctival sickling sign (Paton, 1962) and stromal atrophy of both irides (Galinos, Rabb, Goldberg, and Frenkel, 1973). Ophthalmoscopy of the right eye showed extensive areas of stage I and II retinopathy. The macular area looked normal. Ophthalmoscopy of the left eye showed a recent vitreous haemorrhage occupying the lower temporal quadrant with extensive sea fan neovascularization extending from

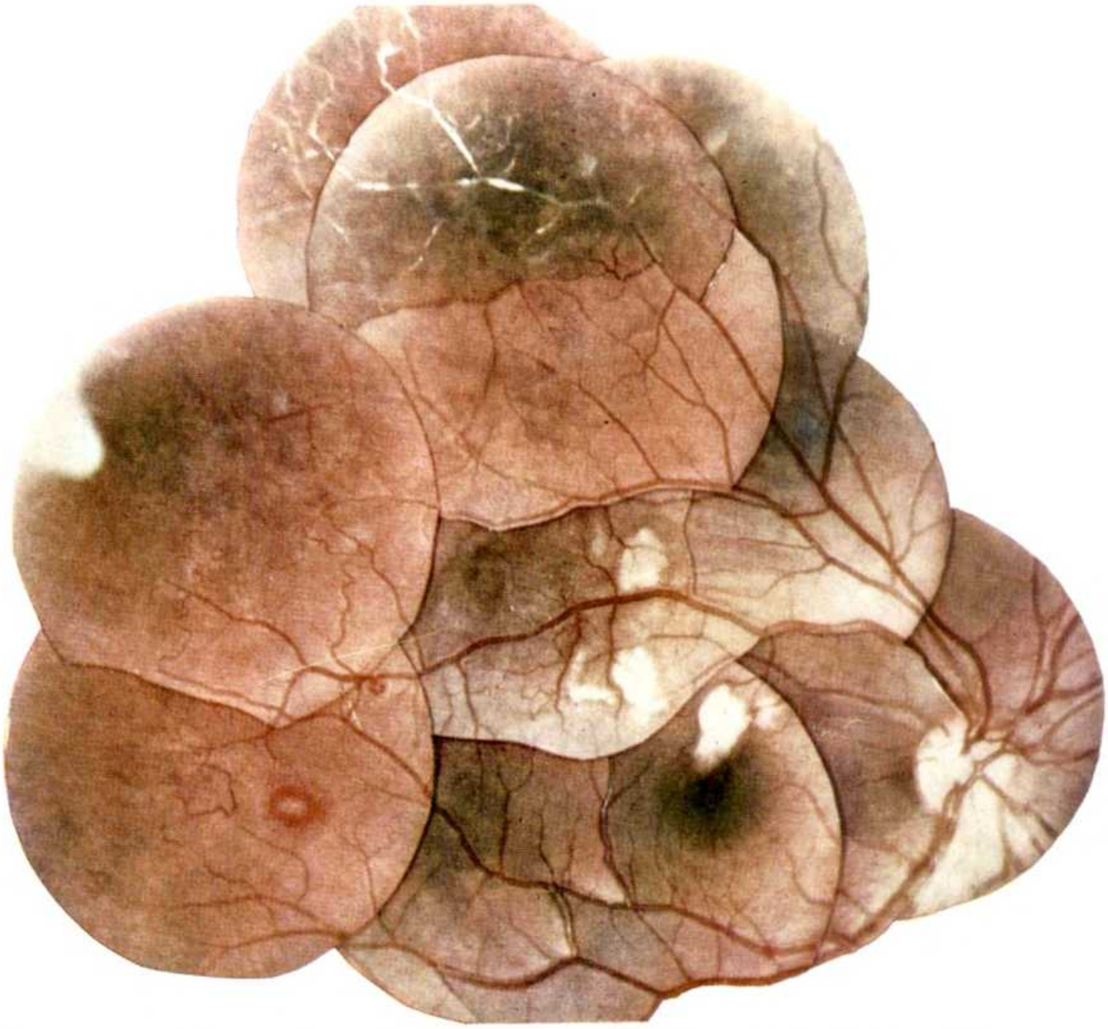


FIG. 2 *Case 1. Right fundus on day cotton-wool patches developed (four days after Fig. 1). Salmon-patch haemorrhage evident at 9 o'clock meridian. Multiple occluded silver-wire vessels present at superotemporal quadrant*

12 to 3 o'clock with evidence of recent haemorrhage. After 24 hours of complete bed rest fluorescein angiography confirmed the presence of stage I and II retinopathy in the right eye with normal macular vasculature (Fig. 1). The left eye showed perfusion and leakage of dye from the previously photocoagulated sea fans.

On the fifth hospital day ophthalmoscopy of the right eye showed cotton-wool patches of the posterior pole (Fig. 2) with one of the patches extending to the superior border of the fovea. The patient had no visual symptoms. Vision was still 20/20. Visual field testing on the tangent screen and with the Goldmann perimeter was normal. Amsler grid testing indicated no scotomas. Colour vision testing was normal with the Ishihara plates and the D-15 panel test. By fluorescein angiography multiple arteriolar occlusions corresponded to the areas of the cotton-wool patches (Figs 3 and 4). At the macular area a single capillary bridged the superior aspect of the foveal avascular zone (FAZ). Forty-eight hours after this acute episode ophthalmoscopy showed no remarkable change. Fluorescein angiography showed persistent closure of all the previously closed arterioles (Fig. 5*a*). The single capillary at the superior border of FAZ was not perfusing at this time (Fig. 5*b*). Retrograde filling of one of the occluded vessels was evident. There was no change in the visual acuity, visual fields, and colour discrimination.

Two months later the patient complained of blurred vision in the right eye, which now had visual acuity of 20/50. There was evidence of a recent vitreous haemorrhage from a newly developed equatorial neovascularization at the 11 o'clock meridian. Fluorescein angiography, which the vitreous haemorrhage obscured somewhat, showed reperfusion of all the previously occluded arteri-

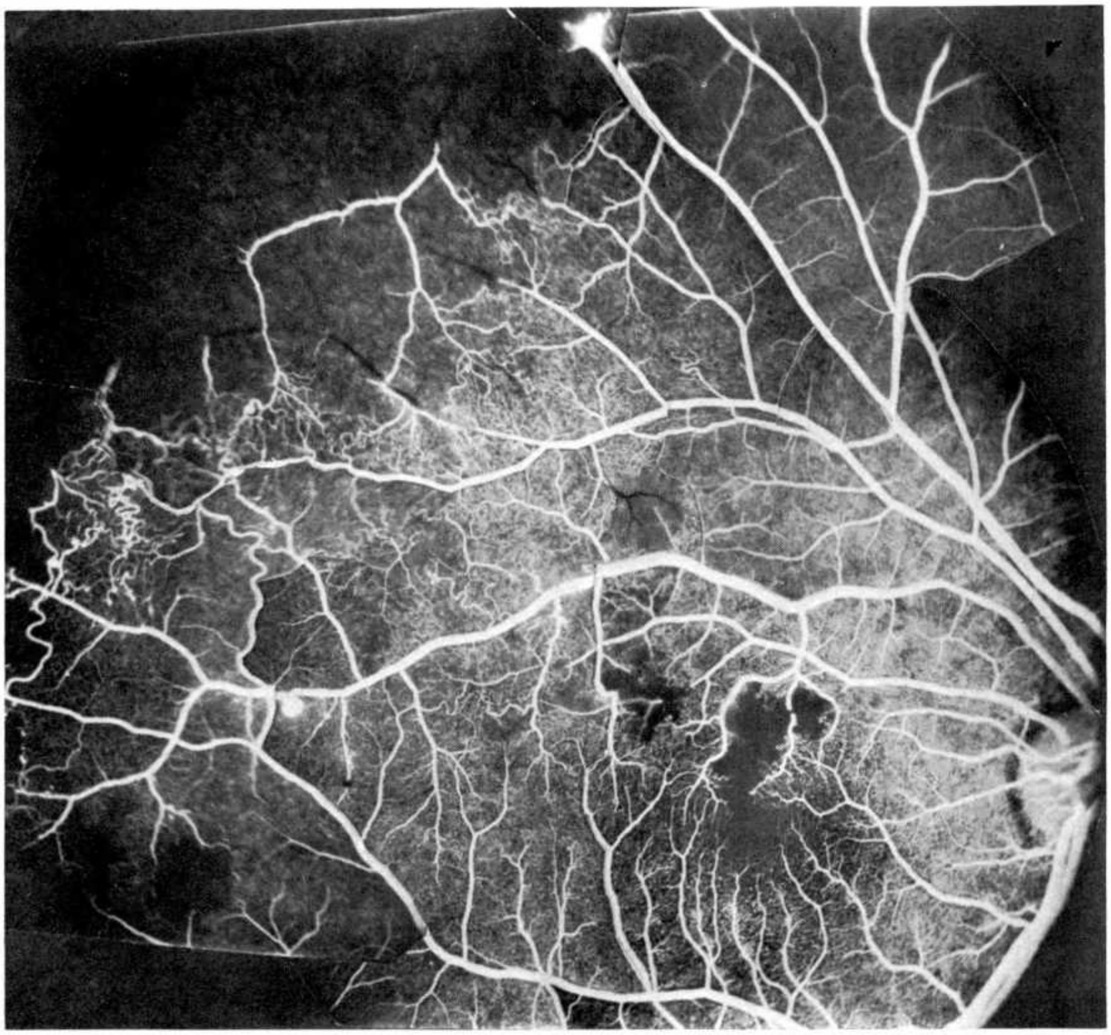


FIG. 3 *Case 1. Fluorescein angiogram of right fundus 48 hours after cotton-wool patches developed. An arteriolar occlusion corresponds to each cotton-wool patch*

oles in the macular region except one (Fig. 6). The capillary at the superior border of the FAZ was reperfusing, and three newly developed venular loops were directed into areas of non-perfused retina (Fig. 6). Five months after the initial acute episode and three months after her last visit visual acuity in the right eye was 20/20. Ophthalmoscopy showed the vitreous haemorrhage to have resorbed completely. The cotton-wool patches had also resorbed (Fig. 7). Their locations could be identified as dimpled facets, probably representing localized areas of retinal atrophy. On fluorescein angiography all except one of the previously occluded arterioles perfused. The capillary beds surrounding the areas of venular loops were more prominent and were directed into areas of capillary bed drop-out (Fig. 8). One capillary clearly separated the FAZ from the adjacent avascular area. One week later, fluorescein angiography showed further changes in the character of the venular loops (Fig. 9).

Case 2

A 30-year-old Black man with sickle-cell anaemia (S 95·4 per cent, A_2 1·7 per cent, F 2·9 per cent) was first seen at the Eye and Ear Infirmary in December 1972 as a screening patient with no visual complaints. Best corrected vision was 20/20 in the right eye and 20/25+ in the left. Both conjunctivas showed fairly numerous sickling signs (Paton, 1962). By ophthalmoscopy the right posterior pole appeared normal. Ophthalmoscopy of the left posterior pole showed several terminal arteriolar segments which were larger

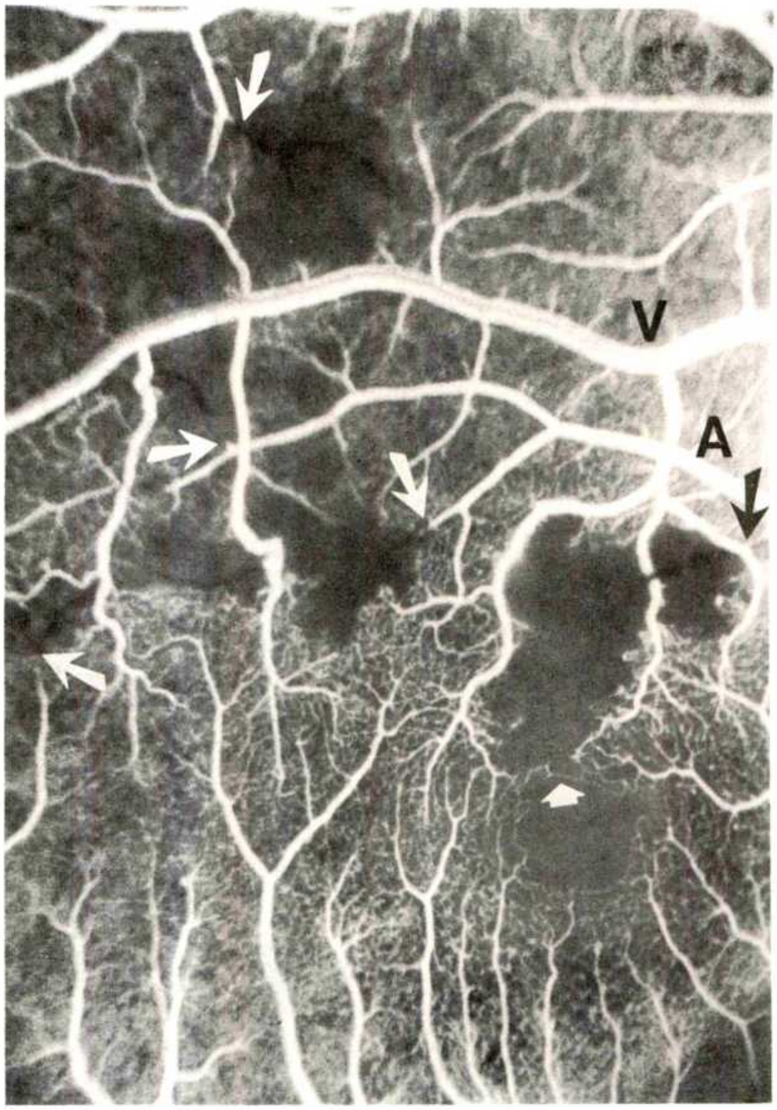


FIG. 4 *Case 1. Fluorescein angiogram of right posterior pole on day cotton-wool patches developed. Longer arrows indicate site of arteriolar occlusions. Dependent vascular beds not perfused. Shorter arrow indicates single capillary bridging superior aspect of FAZ. A, arteriole ; V, venule*

and darker than normal, suggesting obstructed vascular segments. The peripheral retina in both eyes was pale and vessels were thin and sparse. A fibrovascular nodule was seen in the left equatorial zone at the 9 o'clock position.

Fluorescein angiography of the left macular region showed a normal-looking FAZ. Just temporal to the FAZ were three non-filling terminal branches corresponding to the dark segments described above (Fig. 10). The capillary bed surrounding these vessels was sparse. Fluorescein angiography of the right macular area was normal. Visual field testing on the Goldmann perimeter and the tangent screen showed no scotomas, and the responses to the pseudoisochromatic plates and the Farnsworth D-15 panel were normal. Static perimetry with the Goldmann perimeter through the area temporal to the macula showed an absolute scotoma which had not been found with ordinary kinetic perimetry with the Goldmann apparatus or the tangent screen.

Fasting serum glucose level and oral glucose tolerance test were normal, and results of serologic tests for syphilis were normal.

At follow-up examination on 9 April 1974 his visual acuity was the same. The previously dark-coloured arteriolar segments in the left fundus were of normal colour. An arteriolar segment in the right fundus looked darker in colour, suggesting occlusion. By fluorescein angiography the previously occluded vessels in the left eye were perfusing again (Fig. 11) but the capillary meshwork round them remained sparse. In the right eye the dark arteriolar segment seen on ophthalmoscopy was non-perfusing with a sparse capillary meshwork

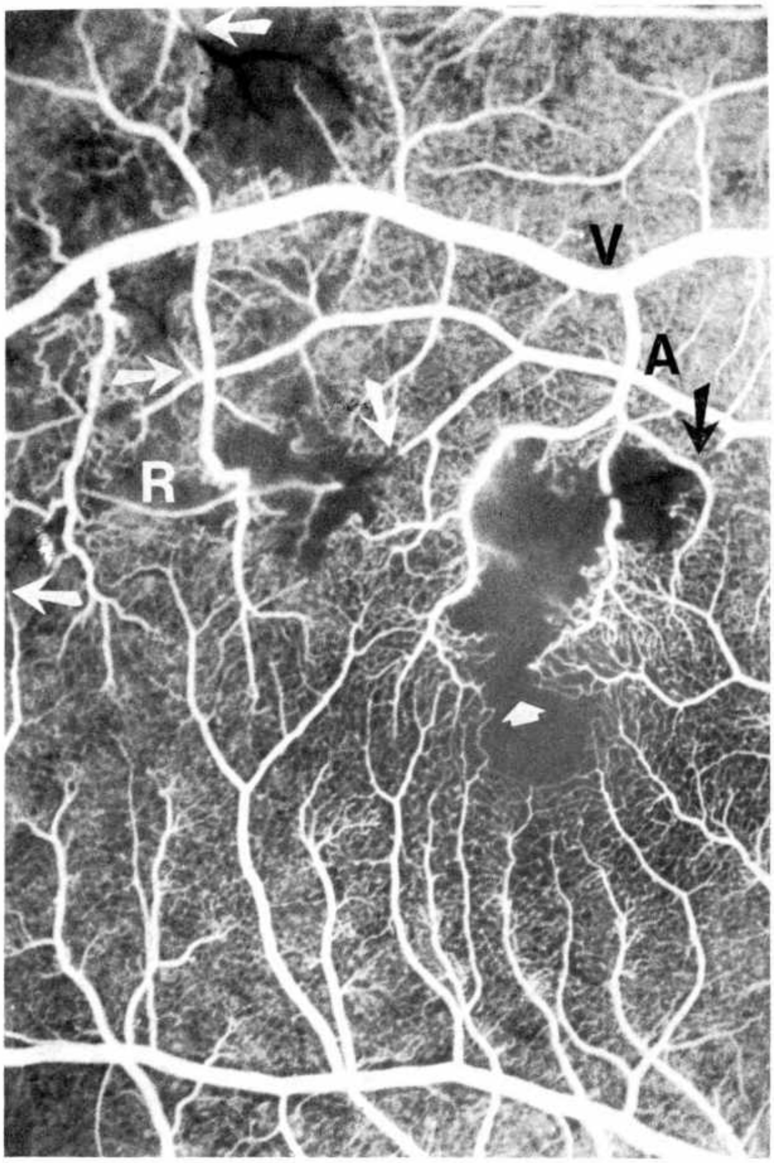


FIG. 5 *Case* 1. *Fluorescein angiograms of right posterior pole 48 hours after acute episode.* (a) *Shows persistent closure of all involved arterioles (longer arrows). Shorter arrow indicates non-perfusion of single capillary bridging superior border of FAZ. R indicates retrograde filling of one of occluded vessels; A, arteriole; V, venule.* (b, opposite) *Enlarged view of FAZ showing non-perfusion of single capillary bridging superior border of FAZ (arrow). Compare with Fig.* 4

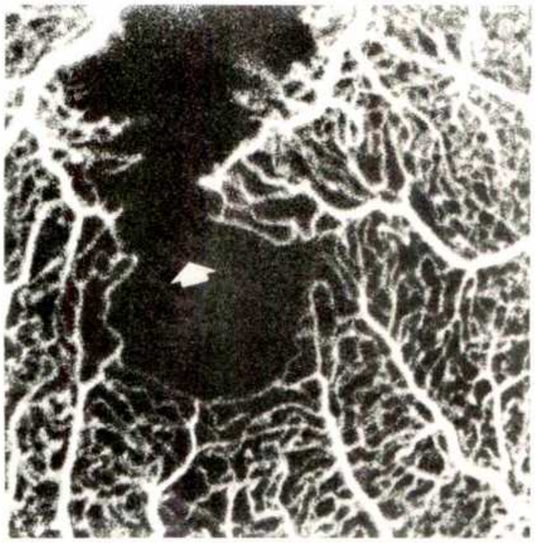
round it. The perifoveal capillary meshwork was also wider than normal, suggesting true capillary loss.

On 18 April the left eye showed no change ophthalmoscopically or angiographically. Ophthalmoscopy of the right eye showed the previously dark arteriolar segment to be of normal colour. Fluorescein angiography showed reperfusion of this previously occluded vessel. However, there was a capillary occlusion at the temporal aspect of the FAZ exaggerating the wide perifoveal capillary mesh.

Case 3

A 24-year-old Black man had sickle-cell anaemia (S 93·3 per cent, F 3·4 per cent, A_2 3·3 per cent) which had been diagnosed at the age of 4. His visual acuity had always been poor and had been much reduced for over 10 years. When first seen in February 1973 in the screening programme at the Eye and Ear Infirmary his best corrected visual acuity was 20/200 in the right eye and 20/400 in the left eye. The conjunctivas showed the sickling sign (Paton, 1962). By ophthalmoscopy both eyes manifested optic atrophy, paucity of the nerve fibre layer on red-free examination, apparently sheathed and possibly occluded macular arterioles, peripheral arteriolar and venular sheathing, and atrophic-looking peripheral retinal tissue.

Fluorescein angiography of the macular regions of



(5*b*)

both eyes showed avascular zones at the centres of the maculae that incorporated and were two to three times larger than the normal FAZ. The blood vessel meshwork surrounding these zones consisted mostly of arterioles and venules connected by large anastomoses. There was loss of the normal fine capillary architecture of these areas. Several non-filling segments were noted at the terminal ends of some arterioles. Kinetic perimetry on the Goldmann perimeter showed a central scotoma of 3 degrees on the right and one of 12 degrees on the left. With the left eye the patient made eight errors on the pseudoisochromatic plates and showed a deutan defect on the Farnsworth D-15 panel. With the right eye his response to the colour tests was normal.

On 27 April 1973 ophthalmoscopy of the left fundus showed a dark-looking segment of the superior temporal arteriole (Fig. 12). Fluorescein angiography showed the dark segment to be occluded (Fig. 13*a*); there were several small vascular occlusions seen ophthalmoscopically. Ophthalmoscopy of the right fundus showed a dark vascular segment of the lower temporal arteriole, and fluorescein angiography showed occlusion of that

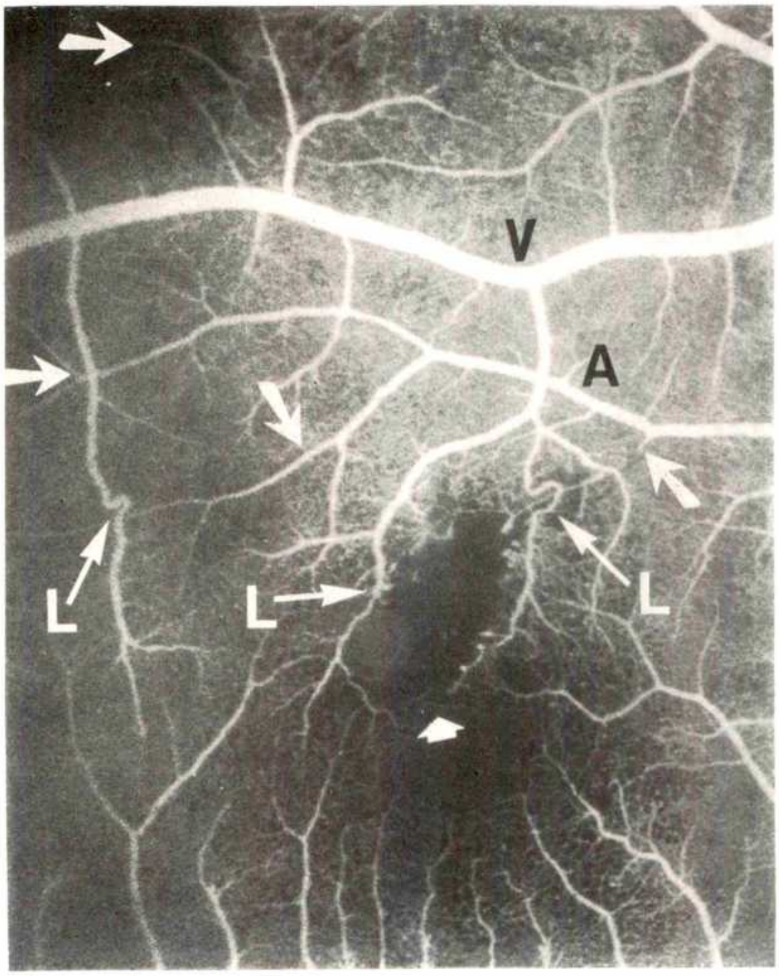


FIG. 6 *Case* 1. *Fluorescein angiogram of right posterior pole two months after acute episode. Vitreous haemorrhage partially obscures view. Longer thicker arrows indicate site of arteriolar occlusions, all except one of which have reopened. Shorter arrow indicates reperfusion of the single capillary at superior border of FAZ. Thinner arrows with L indicate venular loops. A denotes arteriole ; V, venule*

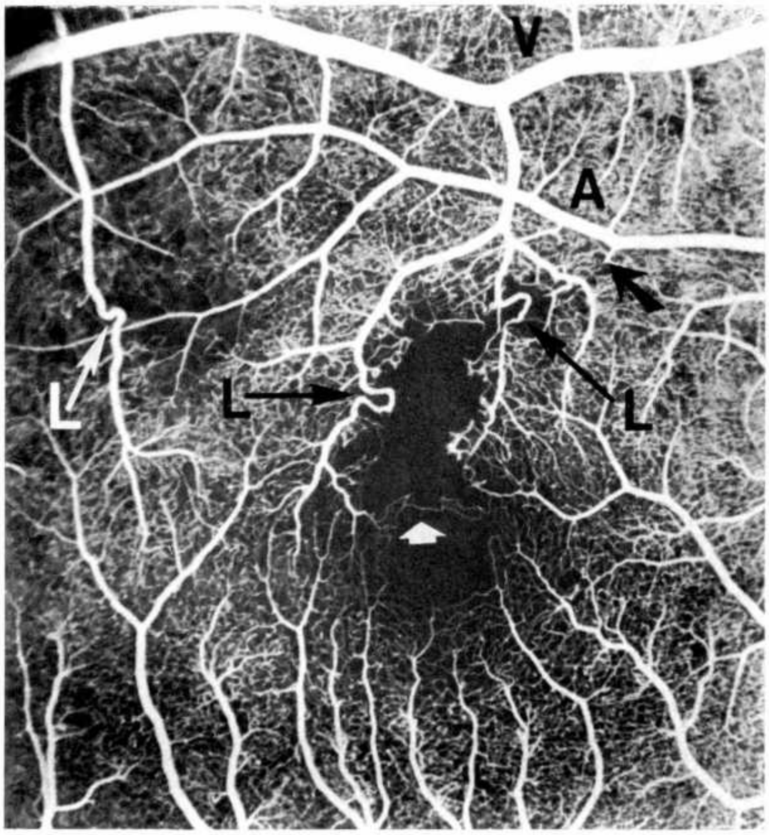


FIG. 8 *Case 1. Fluorescein angiogram of right posterior pole five months after acute episode. All previously occluded vessels are reperfusing except one (longer thicker arrow). Venular loops (thinner arrows with L) more prominent than previously noted. Shorter arrow indicates perfused capillary at superior border of FAZ. A denotes arteriole; V, venule*

segment (Fig. 14*a*). On 28 May 1974, there was no change in his visual acuity. The previously dark-looking segment in each eye was of normal colour by ophthalmoscopy. Fluorescein angiography showed perfusion of the previously occluded vascular segments (Figs 13*b*, 14*b*).

Ophthalmoscopy on 17 June showed a dark vascular segment of the superior temporal arteriole which was larger than the previously noted one. Fluorescein angiography showed occlusion of the previously occluded vessel, but the site of occlusion was more proximal than the previous one and there was an unsuspected small terminal vascular occlusion of the lower temporal arteriole (Fig. 13*c*). Ophthalmoscopy of the right eye showed a dark vascular segment at the site of the previous occlusion. Fluorescein angiography indicated reocclusion of the same segment. There was evidence of retrograde filling of the distal segment of this occluded arteriole (Fig. 14*c*).

Case 4

A 35-year-old Black woman with sickle-cell anaemia (S 97 per cent, A_2 3 per cent) was screened at the Eye and Ear Infirmary on 29 March 1974. She had no visual complaints, although she had been hospitalized on several occasions for painful crises. Her blood pressure was normal. Fasting blood glucose and two-hour postprandial glucose levels were normal, as were the results of serologic tests for syphilis.

Vision was 20/20 in both eyes with no refractive error. The anterior segments were normal. By ophthalmoscopy both fundi showed generalized tortuosity of the retinal vessels. The macular areas looked normal. Fluorescein angiography of the right macular area showed an irregularly shaped FAZ (Fig. 15*a*, *b*) due to arteriolar occlusion at the 2 and 3 o'clock positions with loss of the nasal arcade of the FAZ. Fluorescein angiography of the left macular area showed a round, regular FAZ which was smaller than the right one (owing to loss of capillaries in the right macula). Kinetic visual fields done on the Goldmann perimeter were normal with no scotomas. Colour vision testing with the pseudoisochromatic plates, Farnsworth D-15 panel, Farnsworth-Munsell 100-hue panel, and the anomaloscope gave normal results.

Four months later there was no change in visual acuity or ophthalmoscopic appearance. By fluorescein angiography of the right macular area the FAZ was smaller than at the previous examination. This was owing to reopening of the occluded vessels at the 2 and 3 o'clock positions and the formation of an arcade at the nasal border of the FAZ. A small capillary which was occluded previously was open at this time (Fig. 15*c*).

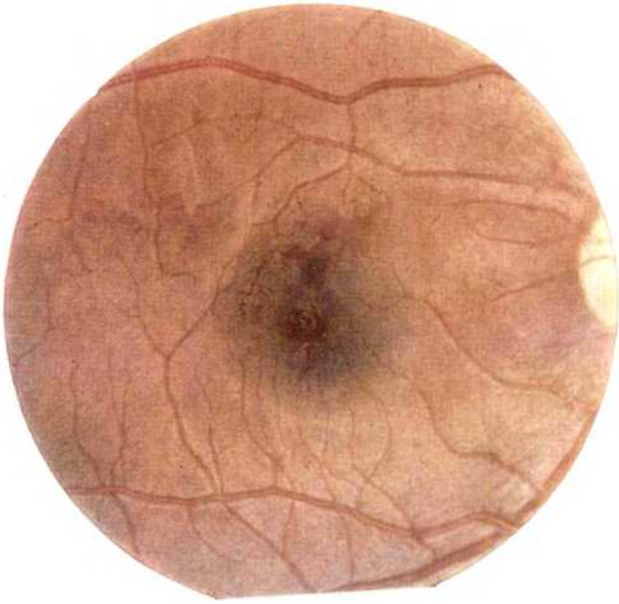


FIG. 7 *Case* 1. *Right posterior pole five months after acute episode. Cotton-wool patches have resorbed*

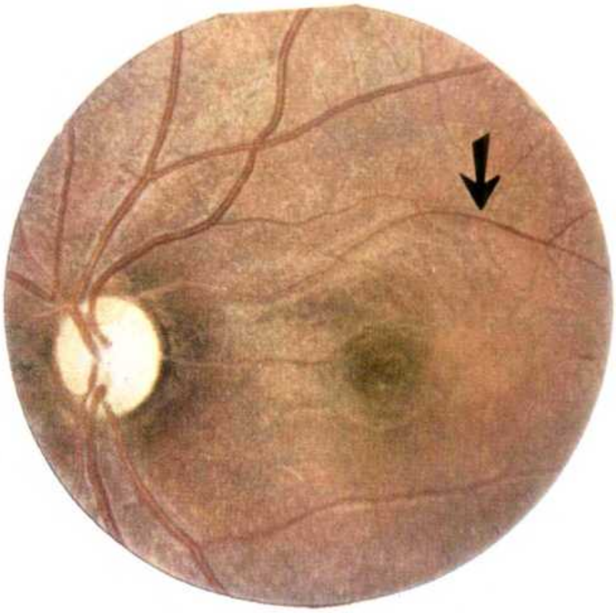
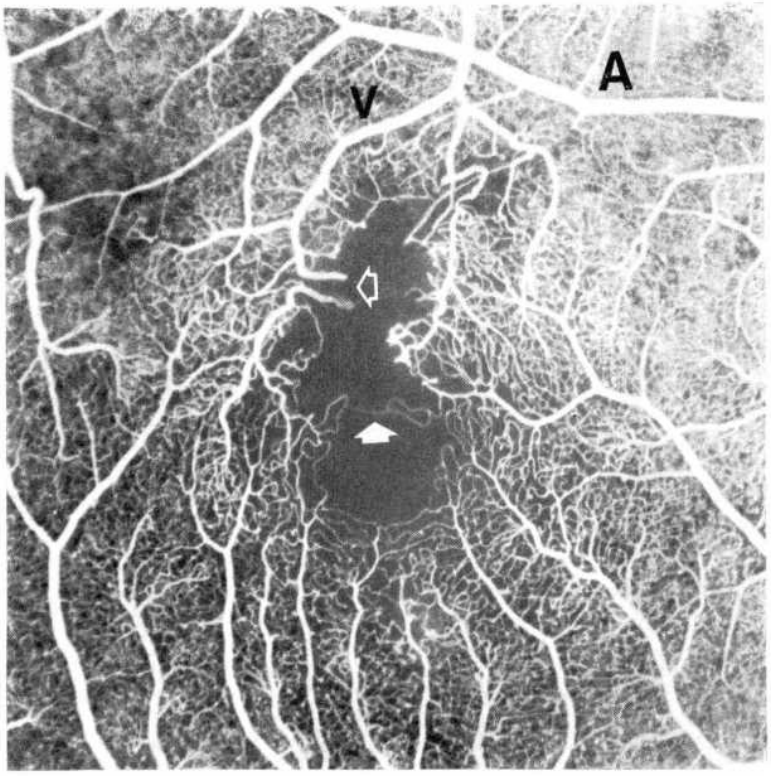
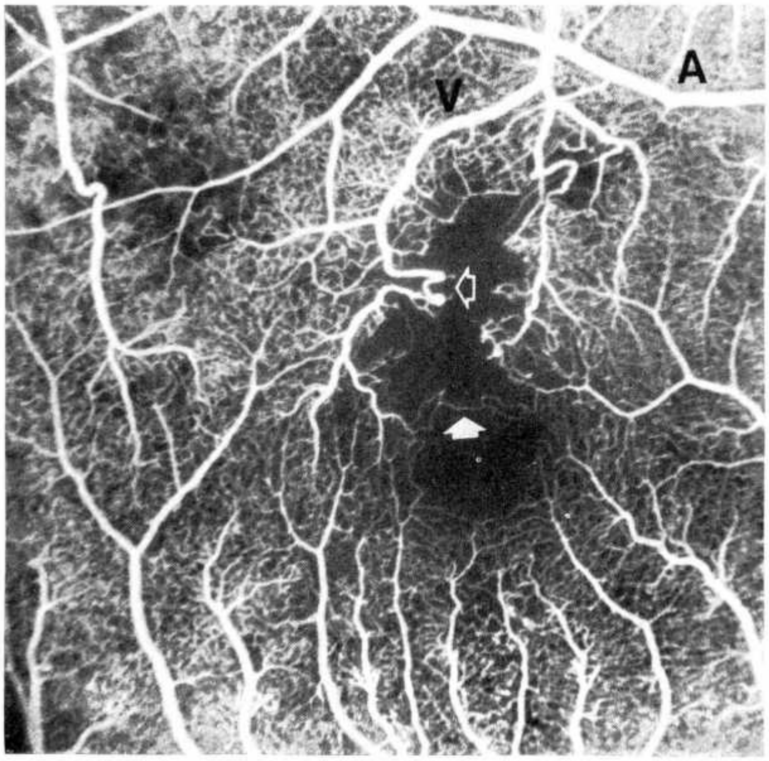


FIG. 12 *Case* 3. *Left fundus showing optic atrophy and a dark-looking segment of upper temporal arteriole* (*arrow*)

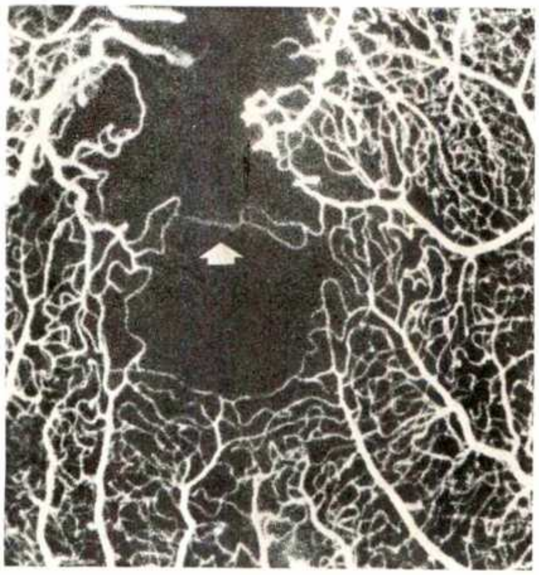


(9*a*)



(9*b*)

FIG. 9 *Case* 1. *Fluorescein angiograms of right posterior pole one week after Figs* 7 *and* 8. (a) *Venular loop (open arrow) is supplied by retrograde filling.* (b) *After complete filling venular loop shows change in shape from previous week.*
(c, opposite) *Enlarged view of posterior pole shows single capillary (solid arrow) bridging FAZ (arrow). A indicates arteriole; V, venule*



(9*c*)

The macular vasculature of the left eye was unchanged.

At examination on 25 February 1975 visual acuity was still 20/20 with no change in her visual field or colour status. Fluorescein angiography of the right macular area showed no change since the previous examination.

Case 5

An 18-year-old Black man with sickle cell-haemoglobin C disease (S 58 per cent, C 42 per cent), was seen at the Eye and Ear Infirmary on 15 June 1973 as a screening patient with no ocular symptoms. Best corrected visual acuity was 20/20 in each eye. There was no conjunctival sickling sign and no iris atrophy. Ophthalmoscopy of the right eye showed a sharply looping terminal venule 1½ disc diameters temporal and slightly inferior to the macula. The left fundus was normal. By fluorescein angiography the vasculature around the FAZ in the right eye was normal. Temporal and slightly inferior to the fovea a terminal venule looped sharply towards a small area where the capillary bed was sparse (Fig. 16*a*). There were no definite vascular occlusions. The fluorescein appearance of the left macular area was normal. On 12 November 1973 ophthalmoscopy of the right eye showed dark terminal segments of the lower temporal raphe area. Fluorescein angiography confirmed occlusion of these terminal vascular segments (Fig. 16*b*). There was a small, unsuspected vascular occlusion at the superior border of the temporal raphe. The left eye was normal. Kinetic perimetry with the Goldmann perimeter and Amsler grid showed no scotomas. Colour vision testing was normal. Fluorescein angiography on 19 November 1973 showed reperfusion of all the occluded vessels. After that the patient was lost to follow-up.

Case 6

A 35-year-old Black woman with sickle cell-haemoglobin C disease (S 54 per cent, C 46 per cent), was seen at the Eye and Ear Infirmary with a history of transient blurring vision in the left eye of several weeks' duration. Best corrected visual acuity was 20/25–2 in each eye. The conjunctivas showed minimal sickling sign (Paton, 1962). The vitreous in the left eye showed peripheral yellowish material suggesting old haemorrhage. The equatorial region of both eyes showed several sea fan neovascular formations.

Fluorescein angiography of the right macular area showed a normal FAZ. The spaces of the surrounding capillary meshwork varied more in size than normal (Fig. 17*a*, *b*). Temporal to the FAZ there was a pathological avascular zone (PAZ) twice as large as the FAZ. The borders of the PAZ showed tiny beads of fluorescence (Fig. 17*a*). Fluorescein angiography of the left macular area showed an enlarged, irregularly shaped FAZ with beads of fluorescence at its superior and temporal borders (Fig. 18*a*).

The tangent screen and Amsler grid examinations showed no scotomas. The patient had normal responses to the pseudoisochromatic plates and Farnsworth-Munsell 100-hue panels.

Examination one year later showed no ophthalmoscopic change in the macular areas. Fluorescein angiography of both maculae showed more loss of capillaries surrounding the FAZ (Figs 17*c*; 18*b*, *c*). There was no change in her visual acuity, fields, or colour discrimination.

Case 7

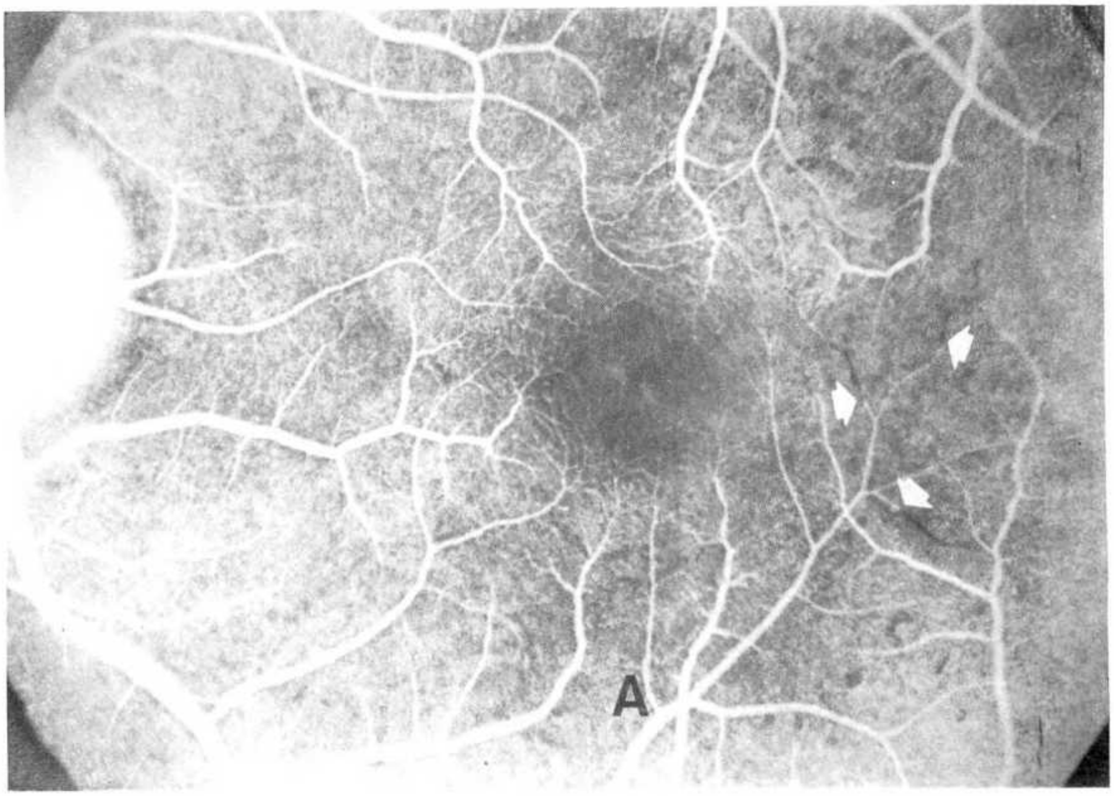
A 45-year-old Black man with sickle cell-haemoglobin C disease (S 53·2 per cent, C 46·8 per cent) was first seen at the Ear and Eye Infirmary on 16 January 1974 as a screening patient. Best corrected visual acuity was 20/30 in each eye. The conjunctivas showed no sickling sign and there was no iris atrophy. Ophthalmoscopy of the right eye showed a neovascular tuft at the 1 o'clock equatorial meridian. The left eye showed several sea fan neovascularizations extending circumferentially around the equator. Both maculae had abnormal vascular patterns with enlarged foveal avascular areas.

Fluorescein angiography of the right macula disclosed an abnormally shaped FAZ with loss of the vascular arcade at the 10 o'clock meridian of the FAZ (Fig. 19). There was a small venular loop directed into the FAZ. The left macular area showed an abnormally shaped FAZ with loss of the vascular arcade at the 7 o'clock meridian (Fig. 20).

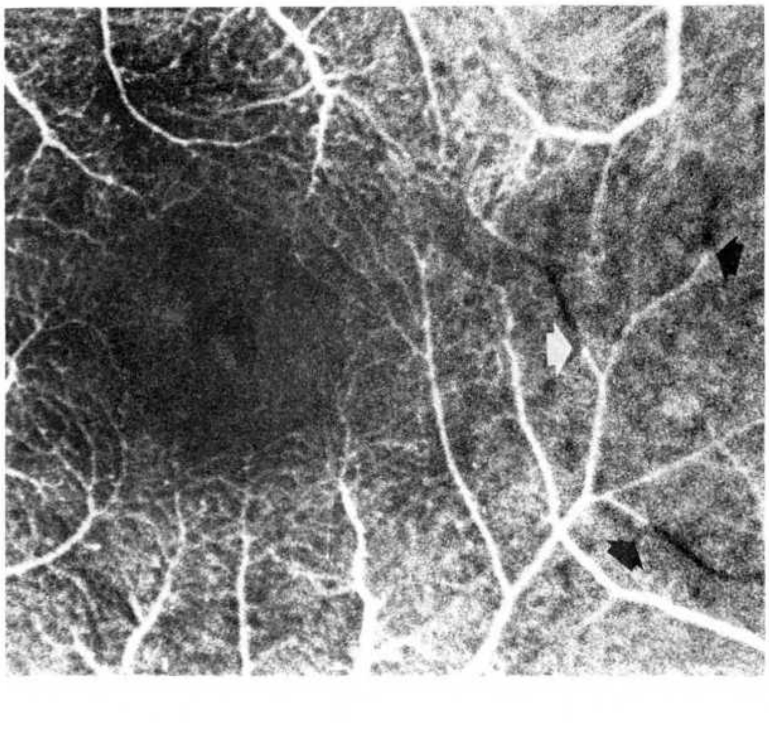
Kinetic visual field testing with the Goldmann perimeter and the Amsler grid manifested no scotomas. Colour vision testing with the pseudoisochromatic plates, Farnsworth D-15, and Farnsworth-Munsell 100-hue panels was normal. During the second year of follow-up the appearance of the left macular area did not change and the character of the venular loop in the right macular area changed somewhat (Fig. 19*b*).

Discussion

Acute vascular changes at the posterior pole in sickle patients have been characterized by central



(10*a*)



(10*b*)

FIG. 10 *Case* 2. *Fluorescein angiograms of left posterior pole.* (a) *Arrows indicate three non-filling terminal segments of same arteriole at temporal raphe.* (b) *Enlarged view of same area. A indicates arteriole*

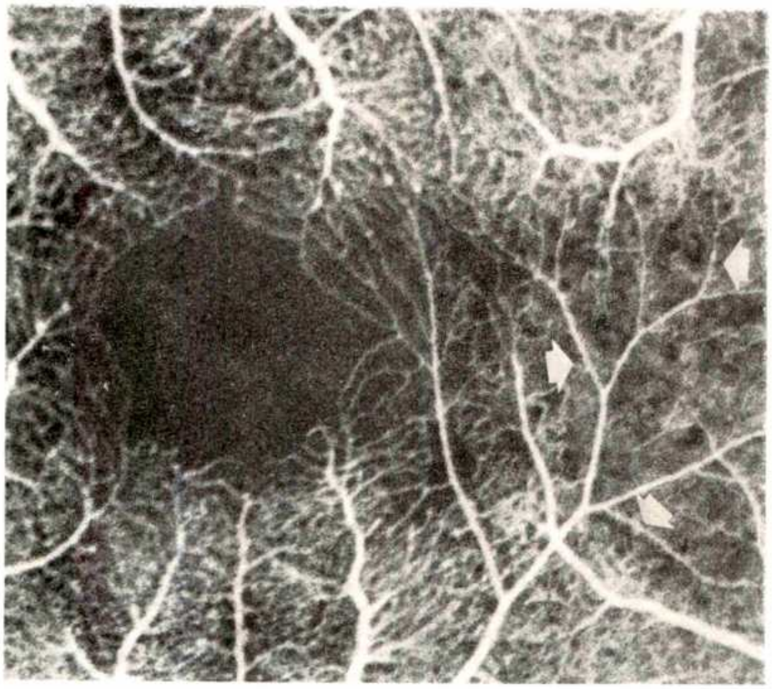


FIG. 11 *Case 2. Fluorescein angiogram of left posterior pole 16 months after initial examination. Previously occluded vessels are perfused (arrows)*

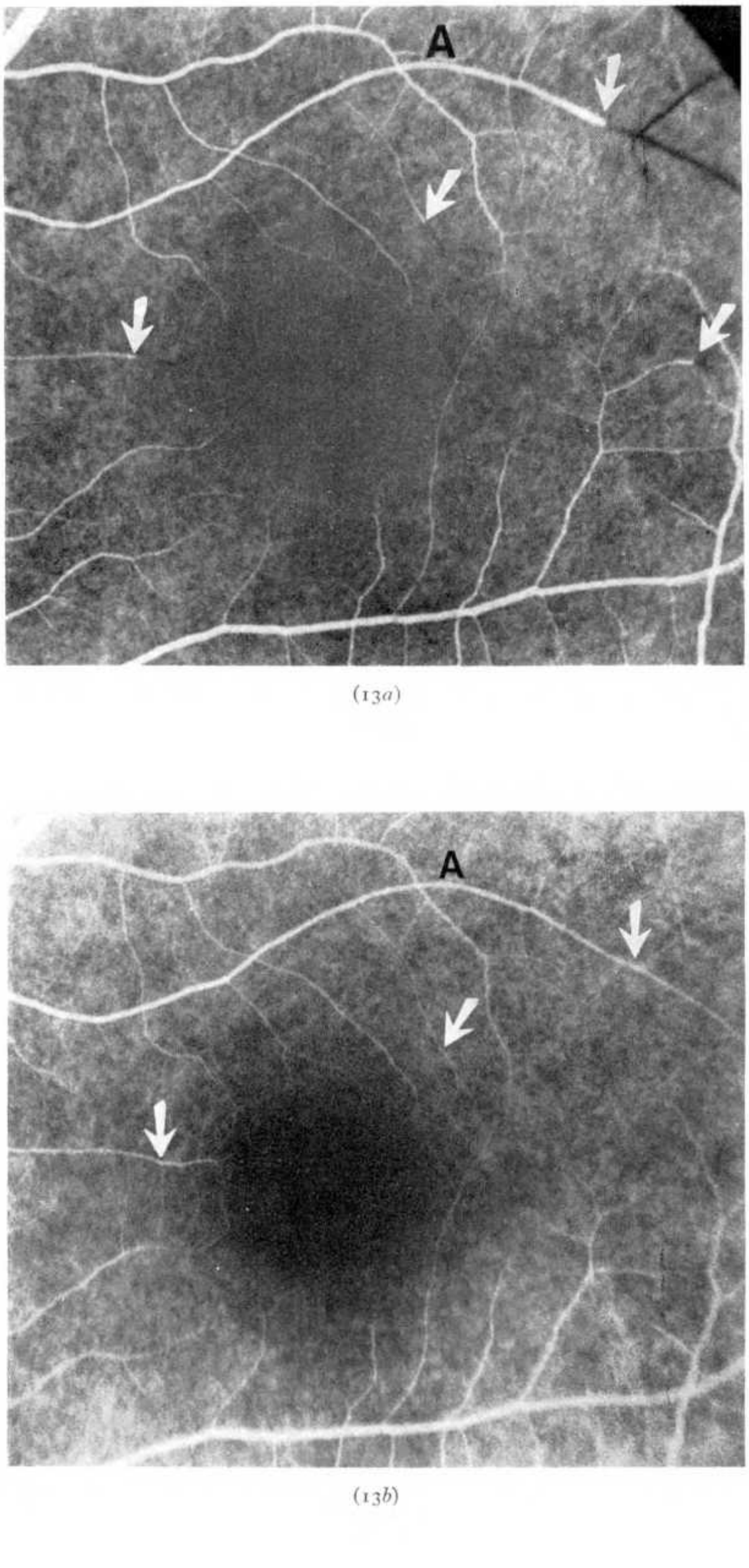
retinal artery occlusions and peripapillary and macular arteriole occlusions (Kabakow, Weimokly, and Lyons, 1955; Conrad and Penner, 1967; Knapp, 1972; Acacio and Goldberg, 1973; Ryan, 1974). Patients with acute vascular occlusion, especially central retinal artery occlusion, usually seek medical advice because of sudden and profound visual loss. Such acute occurrences must be uncommon, however, since only scattered cases have been reported. Branch artery occlusion affecting the macular vessels usually produces central scotomas or loss of vision. Occlusion of fine arteriolar twigs surprisingly may produce no visual disturbances and is therefore not brought to the ophthalmologist's attention. The assessment of the true incidence of these lesions thus becomes difficult.

Chronic abnormalities of the posterior pole have also been reported. Condon and Serjeant (1972a, b, c) reported dilated capillaries and a few microaneurysms of the posterior pole of 10 to 40 per cent of patients, producing no visual symptoms. Since the recognition of chronic macular abnormalities in about 20 per cent of our clinic's population we have examined more carefully the posterior pole of all patients admitted to the clinic using both red-free and direct ophthalmoscopy and selective fluorescein angiography, focusing on the macular vasculature and the area immediately temporal to it.

Out of 100 consecutive patients studied since our initial communication, including some of the originally reported cases, 29 showed some form of posterior pole abnormality—13 with SS haemoglobin, 13 with SC, and three with S-thal. Although vascular occlusions have been reported in patients with AS haemoglobin (Kabakow and others, 1955; Conrad and Penner, 1967), we found no abnormalities in the seven AS patients studied. The posterior pole changes were characterized as microaneurysm-like dots, dark and enlarged segments of arterioles, hairpin-shaped venular loops, pathological avascular zones (PAZ), and widening and irregularities of the foveal avascular zone (FAZ).

In most cases kinetic visual field testing with the tangent screen and Goldmann perimeter did not show any scotomas, even in the presence of large areas of pathological avascular zones. Such preservation of visual function despite lack of normal retinal perfusion has also been described in ischaemic diabetic maculopathy (Kohner, 1971; Bresnick, De Venecia, Myers, and Davis, 1975). Recently we have found that small relative and absolute scotomas can be detected with static perimetry, the scotomas corresponding to these pathological avascular zones.

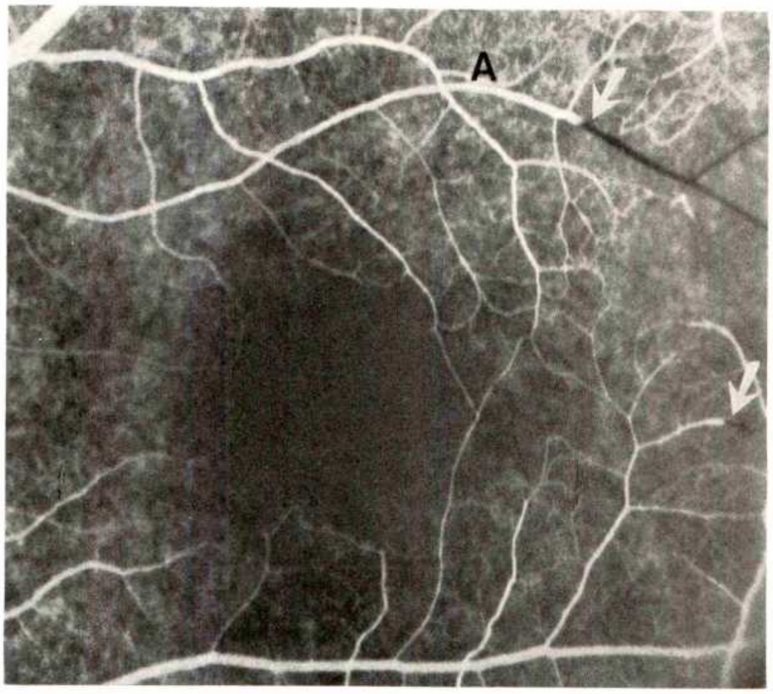
Colour vision seems to be surprisingly well preserved in these patients with posterior pole abnormalities. Although some patients did have colour vision defects, most were normal.



(13*a*)

(13*b*)

FIG. 13 *Case 3. Fluorescein angiograms of left posterior pole.* (a) *Dark segment seen ophthalmoscopically is non-perfusing. Three small occlusions also evident (arrows). FAZ is two to three times larger than normal.* (b) *One year later: all previously occluded vessels are perfusing (arrows).* (c, opposite) *One month later: superior temporal arterioles reoccluded (upper arrow) Site of occlusion is more proximal. Small arteriolar occlusion is evident in a terminal segment of inferotemporal arteriole (lower arrow). A indicates arteriole*



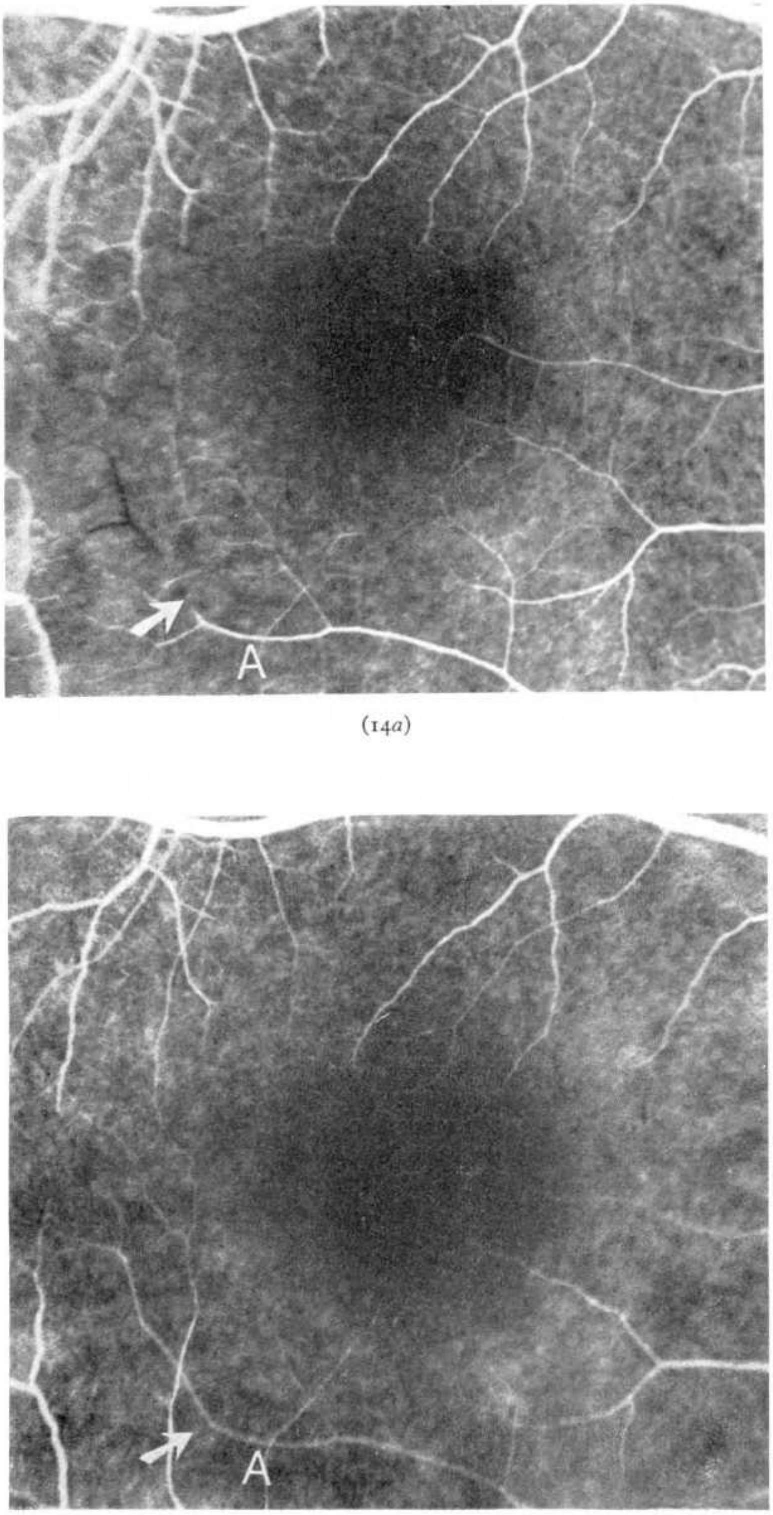
(13*c*)

The discrepancy between the angiographic appearance of the posterior pole vasculature and normal visual function (normal visual acuity, colour vision, and fields) suggests that there may be a considerable redundancy of the blood supply to the macula from either adjacent retinal vascular arcades, the choroid, or both.

Our current tests for evaluating macular function may not be as sensitive for detecting early, minute visual function abnormalities, and thus the need for more sophisticated tests is emphasized. However, with more progressive loss of macular vessels visual function eventually becomes abnormal, as tested by currently available techniques.

Most of these posterior pole abnormalities may be attributable to acute vascular occlusions and their sequelae. For example, case 1 showed vascular changes both in the initial acute episode of vascular occlusion and in the more chronic state when some capillaries still were not perfused. The initial pathogenetic event is arteriolar vaso-occlusion. Although primary venous occlusions may occasionally occur, most occlusions in sickling patients occur on the arterial side of the retinal vasculature. Evidence has accumulated recently to show that deoxygenation of blood may occur in the small arteries to a level that is capable of inducing sickling and causing arteriolar occlusions (before the circulating erythrocytes reach the level of the capillaries and the venules) (Harris, Brewster, Ham, and Castle, 1956; Duling and Berne, 1971). Retinal occlusions may occur in the small arterioles themselves or may be the result of 'log-jamming' in capillaries and 'back stasis' from the sickled cells. Arterial occlusions are not unique to the retinal vasculature as they have occurred in large cerebral arteries (Stockman, Nigro, Mishkin, and Oski, 1972), including the common carotid artery, though larger arteries probably occlude by a different mechanism.

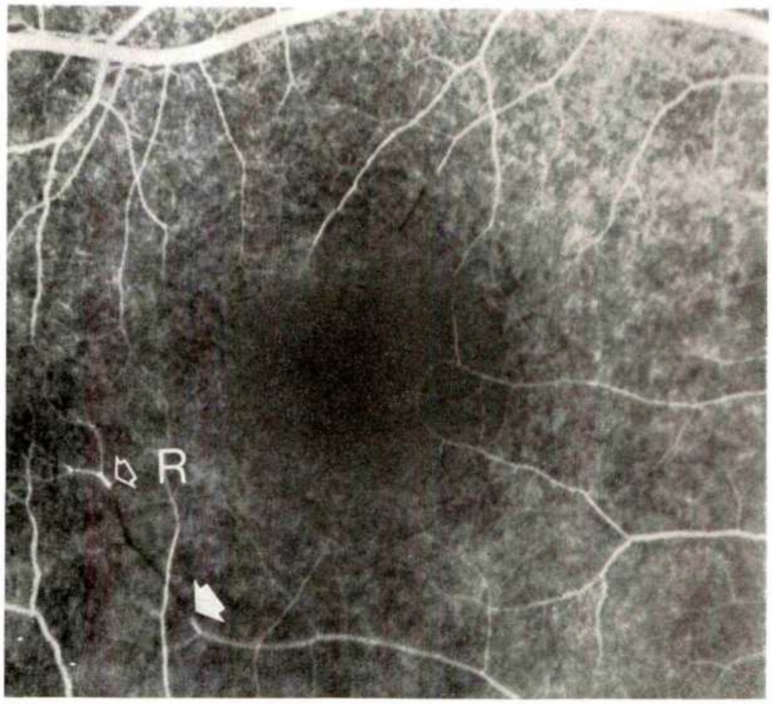
With sudden arteriolar occlusion, when immediate restoration of flow does not occur, a localized area of retinal ischaemia results which is sometimes seen ophthalmoscopically as a cotton-wool patch. Several cotton-wool patches, each corresponding to arteriolar occlusions, were noted in case 1 and were clearly defined by fluorescein angiography. Fluorescein staining of the vessel wall at this stage may denote endothelial damage due to the intraluminal plugs of sickled erythrocytes. To our knowledge, this is the first report of acute arteriolar occlusion resulting in cotton-wool patches in a patient with sickling haemoglobinopathy. These patches represent localized areas of ischaemic necrosis of the inner retinal layers, predominantly the nerve fibre layer. That these lesions occur from occlusion of the precapillary arterioles and adjacent capillaries has been documented in patients with hypertensive and diabetic retinopathy (Esmann, Lundbaek, and Madsen, 1963; Kohner, Dollery,



(14*a*)

(14*b*)

FIG. 14 *Case 3. Fluorescein angiograms of right posterior pole.* (a) *Dark segment seen ophthalmoscopically is not perfusing (arrow).* (b) *One year later: reperfusion of same segment (arrow).* (c, opposite) *One month later: reocclusion of same segment (arrow). Retrograde filling is evident (R). A indicates arteriole*



(14*c*)

and Bulpitt, 1969; Wise, Dollery, and Henkind, 1971).

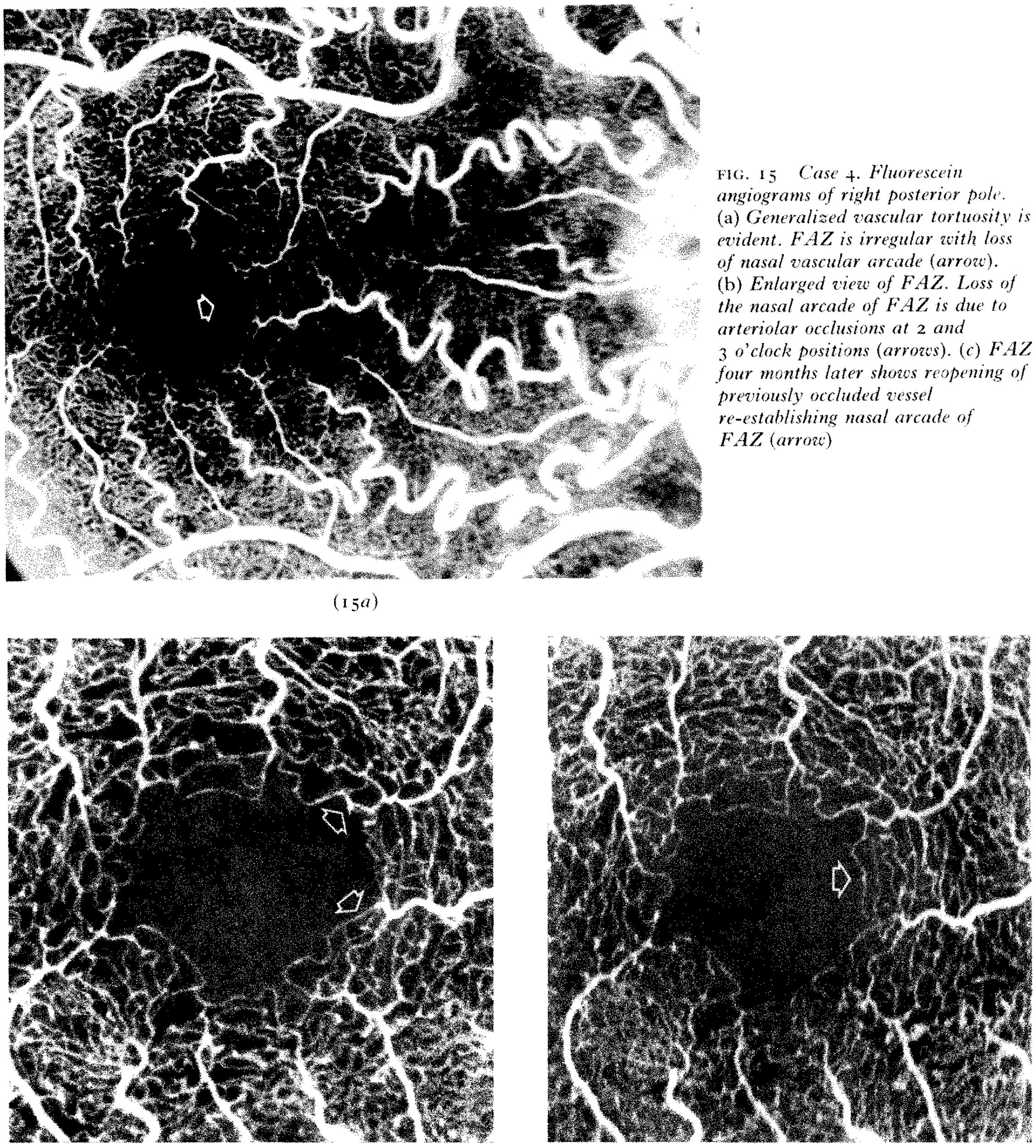
Although ischaemia is the major factor responsible for cotton-wool patches, some of these lesions may occasionally be the result of generalized endothelial damage and vascular leakage (Hodge and Dollery, 1964). In our patient, however, the lesions clearly resulted from acute arteriolar occlusions, since each localized patch corresponded precisely to the dependent capillary bed of an occluded arteriole. Angiography showed no leakage at these sites.

Although cotton-wool patches, if large enough, are associated with local scotomas, our patient did not complain of any visual impairment and her visual acuity, fields, and colour perception were all normal. Possibly the posterior pole abnormalities of many sickle-cell patients start with similar acute episodes and yet, because of lack of visual symptoms, are not seen by the ophthalmologist.

Subsequent to the occlusions the capillary bed dependent on this occluded arteriole is not completely perfused. This non-perfusion does not necessarily mean complete and permanent closure of the capillary bed, and many capillaries may remain patent. Indeed, in pathological specimens they may appear patent although unfilled with erythrocytes. Non-perfusion during ischaemia may be secondary to several factors, including total vaso-occlusion, low perfusion pressure, high tissue pressure with capillary closure secondary to swelling of retinal tissue, capillary contraction or collapse, and endothelial swelling. Depending on the combination and course of these factors, the occluded capillaries reopen or remain non-perfused. In the latter state the areas represent finally the pathological avascular zones that are apparent angiographically. Eventually the cotton-wool spots disappear with return of normal retinal transparency, although their locations sometimes can be identified as localized dimples or facets.

Follow-up examination after the initial acute attack shows multiple vascular changes. The initial area of occlusion may remain non-perfused. Distal to this occlusion a low pressure area may develop. Blood from neighbouring capillaries may flow into this low pressure zone, and fluorescein angiography shows retrograde dye filling (Figs 5, 14*c*). The occluded vessel may reperfuse completely. The dependent capillary bed may re-establish circulation or remain non-perfused. The failure of the capillary bed to reperfuse after establishment of flow in an occluded arteriole and the return of retinal transparency probably indicate postnecrotic atrophy of the inner retinal layers, including the capillary bed, as has been shown by trypsin-digestion and other histopathological techniques (Kornzweig, Eliasoph, and Feldstein, 1964; Kuwabara and Cogan, 1965).

Interesting vascular changes, especially on the



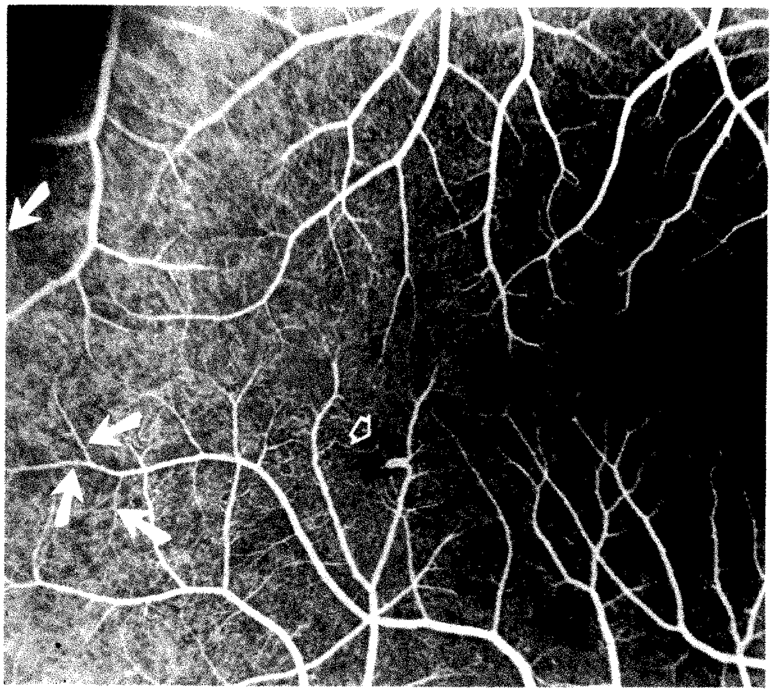
(15*a*)

(15*b*)

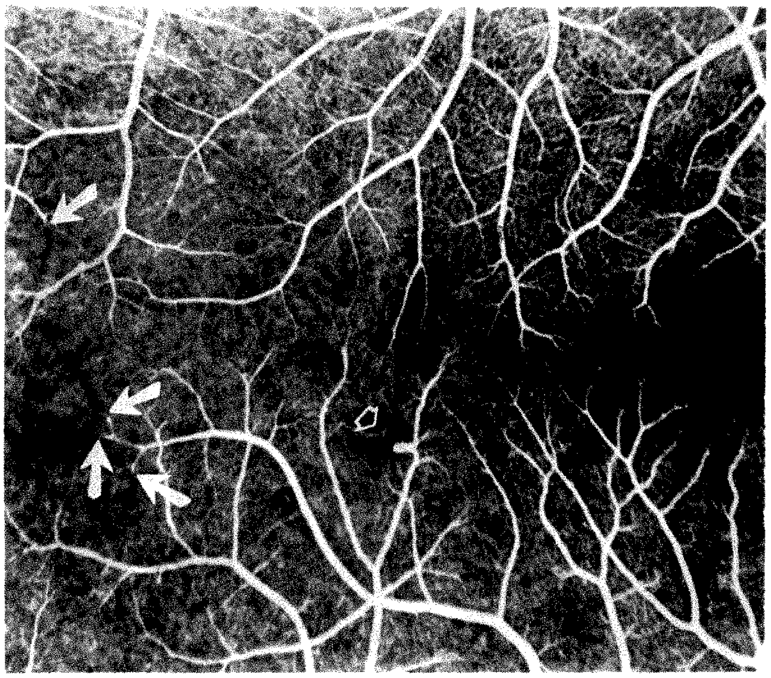
(15*c*)

FIG. 15 *Case 4. Fluorescein angiograms of right posterior pole.* (a) *Generalized vascular tortuosity is evident. FAZ is irregular with loss of nasal vascular arcade (arrow).* (b) *Enlarged view of FAZ. Loss of the nasal arcade of FAZ is due to arteriolar occlusions at 2 and 3 o'clock positions (arrows).* (*c*) *FAZ four months later shows reopening of previously occluded vessel re-establishing nasal arcade of FAZ (arrow)*

venular side, occur adjacent to retinal areas where the capillary bed remains non-perfused. Venular loops develop and are almost always directed into areas of avascular retina. The significance of these loops is not currently understood. Similar venular hairpin-loop configurations have also been noted in diabetes mellitus. Haemodynamic, chemotactic, or even mechanical factors may play a role in the initiation of these vascular loops. It is possible that the intraluminal pressure pushes the vessel into this necrotic, atrophic zone where low tissue pressure may prevail. It may be that the ischaemic area produces a chemotactic factor that induces the growth of vessels into it, the first step in neovascularization. It is also possible that change is induced in the internal limiting membrane or

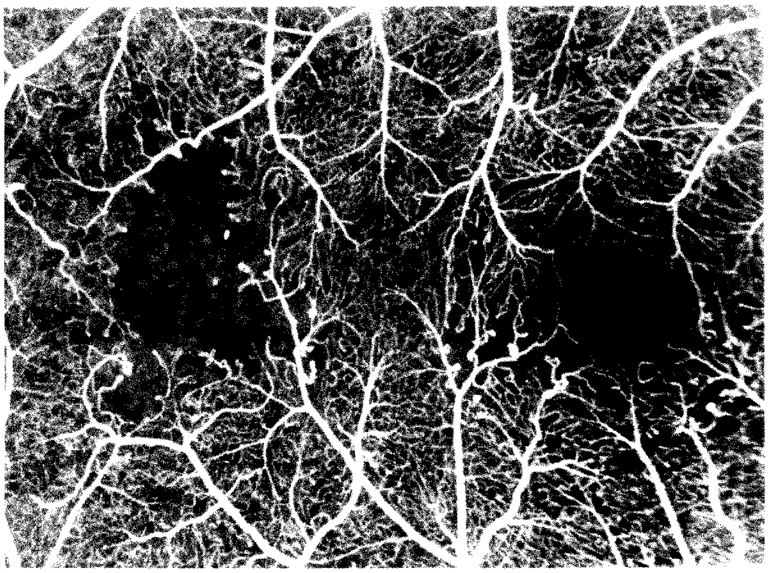


(16*a*)



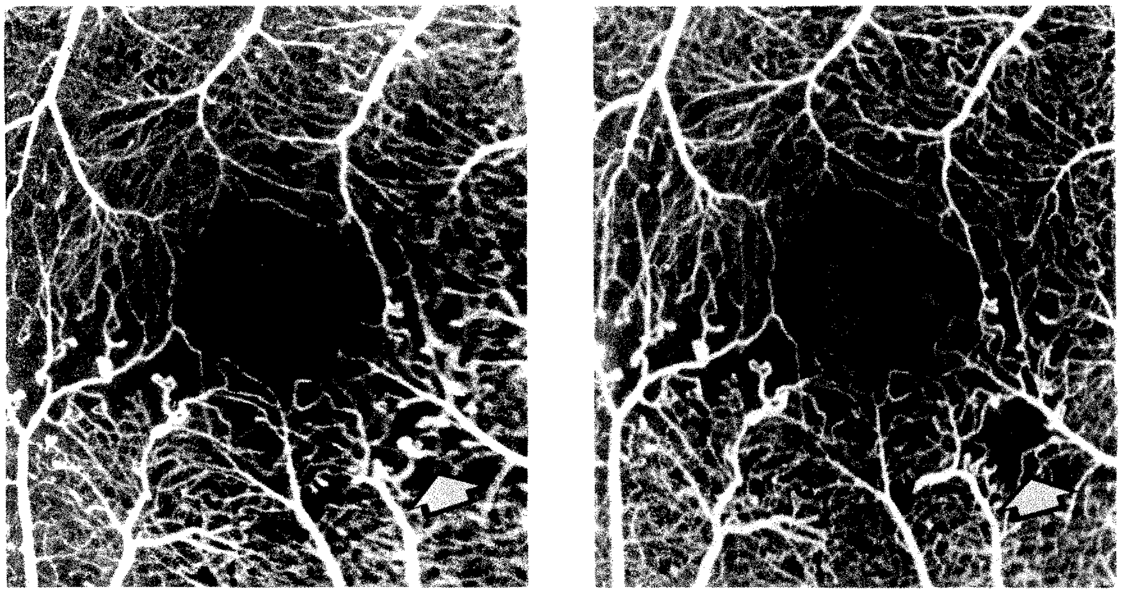
(16*b*)

FIG. 16 *Case* 5. *Fluorescein angiograms of right macular area and area temporal to it.* (a) *Shorter arrow indicates venular loop directed into area with sparse capillaries. Longer arrows indicate reference vessels that occluded five months later and are seen in* (b)



(17*a*)

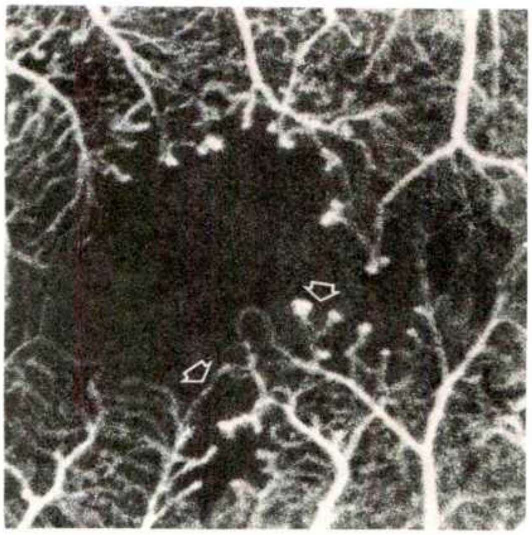
FIG. 17 *Case* 6. *Fluorescein angiograms of right posterior pole.* (a) *Beads of fluorescein are apparent in the capillaries surrounding the FAZ. Temporal to the FAZ is a PAZ.* (b) *Enlarged view of the FAZ. The spaces of the surrounding capillary meshwork are more variable in size than normal. Arrow shows area where further capillary loss occurred* (*see* (c)). (c) *One year later, further loss of capillaries surrounding FAZ* (*arrow*)



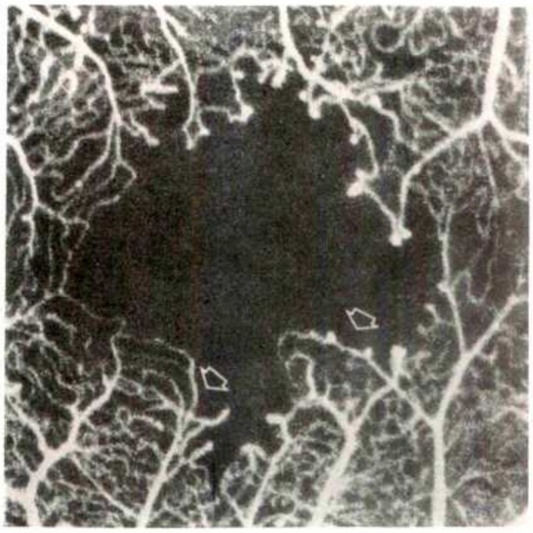
(17*b*) (17*c*)

other tissues which may mechanically pull the vessel in. All these are theoretical possibilities and more than one factor may be operative.

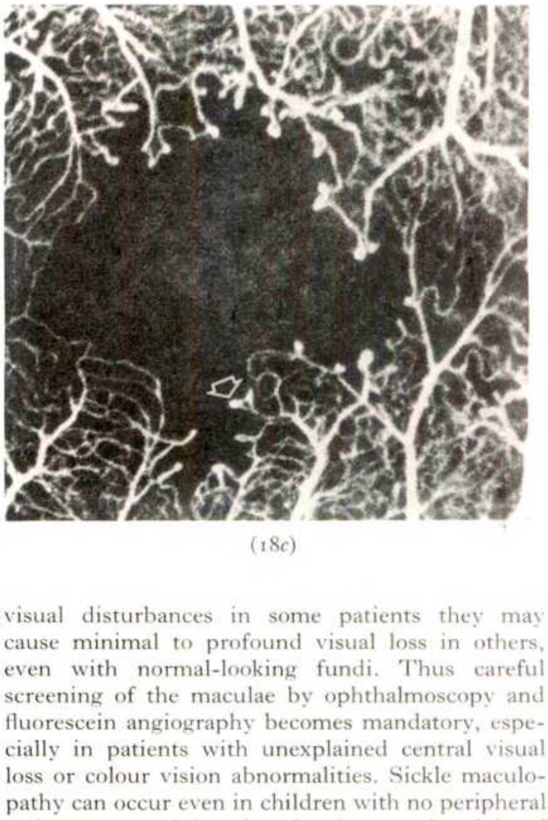
The maculopathy that starts with acute occlusions usually follows a chronic progressive course with larger and more numerous areas of the retina gradually becoming involved. Fluorescein angiography repeated at intervals of several months shows a continuous remodelling of the retinal vasculature of the posterior pole. Occlusions may extend posteriorly or completely reopen (Fig. 13). Pathological avascular zones become larger and foveal avascular zones may change size and shape. Occasionally a reverse process may ensue, an avascular zone may become revascularized and an abnormal foveal avascular zone may revert to normal size and configuration (Fig. 15*b*, *c*). It is important to observe the patients regularly to recognize this



(18*a*)



(18*b*)



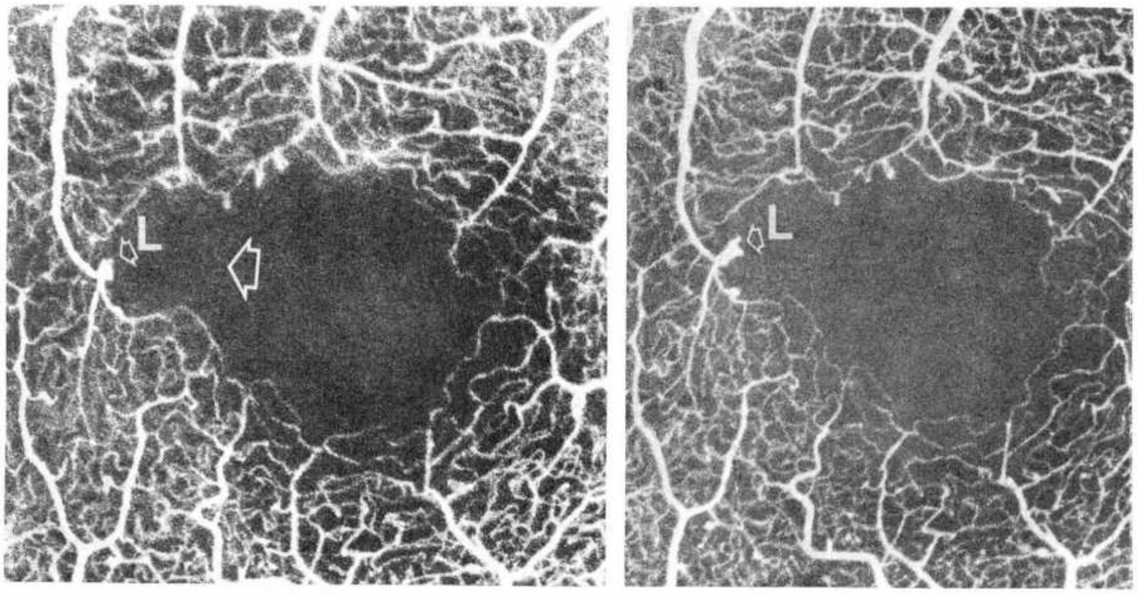
(18*c*)

FIG. 18 *Case 6. Fluorescein angiograms of left posterior pole.* (a) *Irregularly shaped FAZ with loss of capillaries accentuated at its temporal border. Beads of fluorescein are evident. Arrows indicate sites of future occlusions.* (b) *At follow-up six months later: further occlusions at the 5 and 7 o'clock areas (arrows) have enlarged FAZ.* (c) *15 months later: single capillary reopened at 6 o'clock meridian (arrow)*

continuous remodelling in the vasculature of the retina. The arterioles may plug and unplug and the dependent microvasculature may change accordingly. This phenomenon of continuous opening and closing of the affected vessels supports the view that there is a mechanical type of obstruction caused by aggregates of impacted sickle cells rather than a real thrombosis, but recanalization of a true thrombosis may also occur.

Such complex remodelling of the retinal vascular bed as the result of vascular occlusion is not unique to the posterior pole. We have recently reported similar vascular remodelling in the peripheral vasculature of patients with different sickling haemoglobinopathies (Galinos and others, 1975). Harnish and Pearce (1973) also reported retinal vascular remodelling in non-sicklers with hypertensive retinal vascular disease. Their observations were similar to ours in that vascular occlusions were followed by a complex remodelling of the retinal vasculature, a process which continued over a period of years.

The clinical implications of the posterior pole abnormalities are manifold. Although some of the vascular abnormalities do not cause any detectable visual disturbances in some patients they may cause minimal to profound visual loss in others, even with normal-looking fundi. Thus careful screening of the maculae by ophthalmoscopy and fluorescein angiography becomes mandatory, especially in patients with unexplained central visual loss or colour vision abnormalities. Sickle maculopathy can occur even in children with no peripheral retinopathy, and therefore the absence of peripheral lesions does not preclude the need for careful assessment of the macula. Finally, these changes may in the future serve as indicators in the evaluation of systemic therapeutic regimens to minimize the sickling process and improve blood flow.



(19*a*) (19*b*)

FIG. 19 *Case 7. Fluorescein angiograms of right posterior pole.* (a) *Abnormally shaped FAZ with loss of vascular arcades at 9 to 10 o'clock meridian (arrow). L denotes venular loop directed into avascular zone.* (b) *Further changes in character of venular loop one year later*

Summary

The posterior pole vasculature of 100 patients with different sickling haemoglobinopathies was studied prospectively over a period of three years. Various abnormalities of the posterior pole vasculature were seen in 29 per cent of the patients. Continuous remodelling of the macular and perimacular vasculature occurred. Visual acuity was variably affected and sometimes remained intact.

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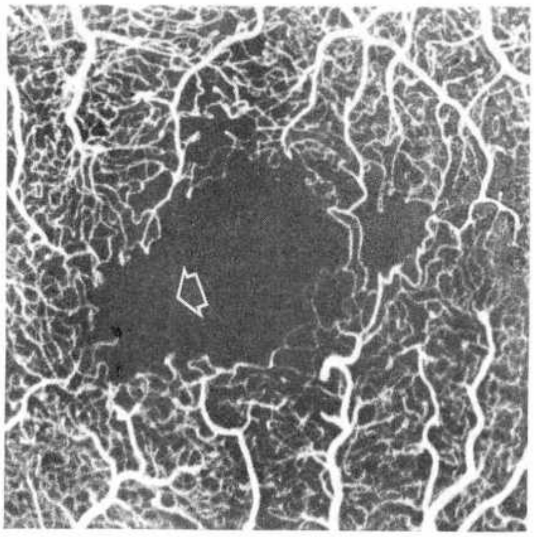

FIG. 20 *Case 7. Fluorescein angiogram of left posterior pole with abnormally shaped FAZ. Loss of vascular arcade of 7 o'clock meridian (arrow). Island of PAZ present at 2 o'clock meridian*

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Acute vitreous haemorrhage: a clinical report

HARVEY LINCOFF, INGRID KREISSIG, AND MURRAY WOLKSTEIN
From New York

Acute vitreous haemorrhage presents to the patient as a sudden onset of black spots, followed by rapid clouding of vision as the blood disperses through the media. The ophthalmoscopic picture varies from a loss of retinal detail to a loss of fundus reflex, depending on the quantity of blood released.

Biomicroscopy of the vitreous is revealing because blood cells collect on the surface of the vitreous membranes and membranelles and provide a kind of *in vivo* staining of vitreous structures. Vitreous membranes appear to be impermeable to red blood cells. When detachment of the posterior hyaloid provokes a retinal haemorrhage the post-hyaloid space fills with blood. Red blood cells coat the external surface of the hyaloid but the internal surface and the vitreous gel remain clear (Fig. 1).

The retrohyaloid space is an aqueous-filled chamber and eye movements maintain red blood cells in it in diffuse suspension. If the eye movements are diminished, however, by binocular patching and the patient is maintained with his head raised, the blood cells gravitate to the bottom of the space and collect as a meniscus at the inferior vitreoretinal insertion (Fig. 2*a*, *b*). This occurs within hours. There is a small convection current, due to the relative warmth of the retinal surface as opposed to the hyaloid membrane, but it is too small to overcome the gravitational pull.

Blood eventually enters the vitreous gel by way of holes that develop in the posterior hyaloid, usually in the days immediately following the haemorrhage. Eisner (1973) has observed these holes in cadaver eyes. They start as a tearing of the hyaloid at the edge of the disc and become round as the membrane separates from the disc and the gel prolapses through the holes (Fig. 3*a*, *b*). Blood cells migrate into the gel with eye movements and collect on the membranelles, making the pattern of prolapse visible. More than one hole may form (Fig. 4) and they may enlarge and expand all the way to the bottom of the eye (Fig. 5).

The selection of patients who will respond to binocular occlusion and positioning may be based upon the biomicroscopic examination. If the blood is confined behind the posterior hyaloid membrane and the vitreous gel is free of cells settling may be predicted with some certainty and a view of the retina will become available within hours. If, however, the gel is already infiltrated with cells and they are dense enough to obscure the hyaloid membrane occlusion and positioning will not result in significant clearing, for cells in the gel do not settle. If the hyaloid can be perceived at all a trial is indicated.

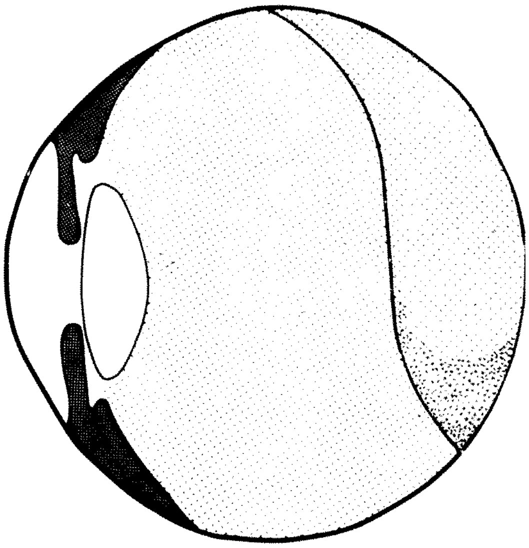
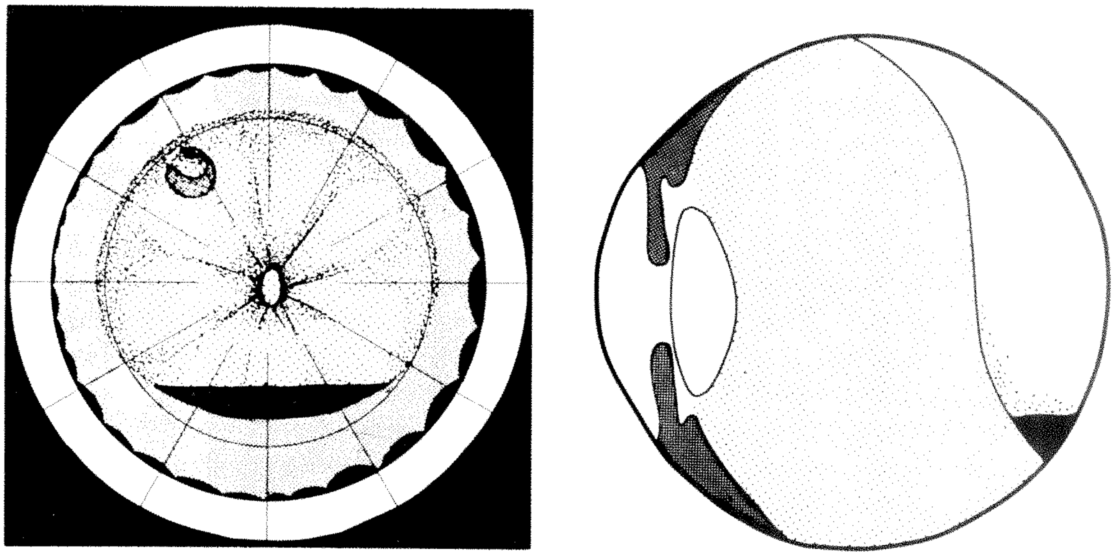


FIG. 1 *Blood diffused in retrohyaloid space after acute haemorrhage. Red blood cells coat external surface of hyaloid but internal surface and vitreous gel remain clear*

Patients and methods

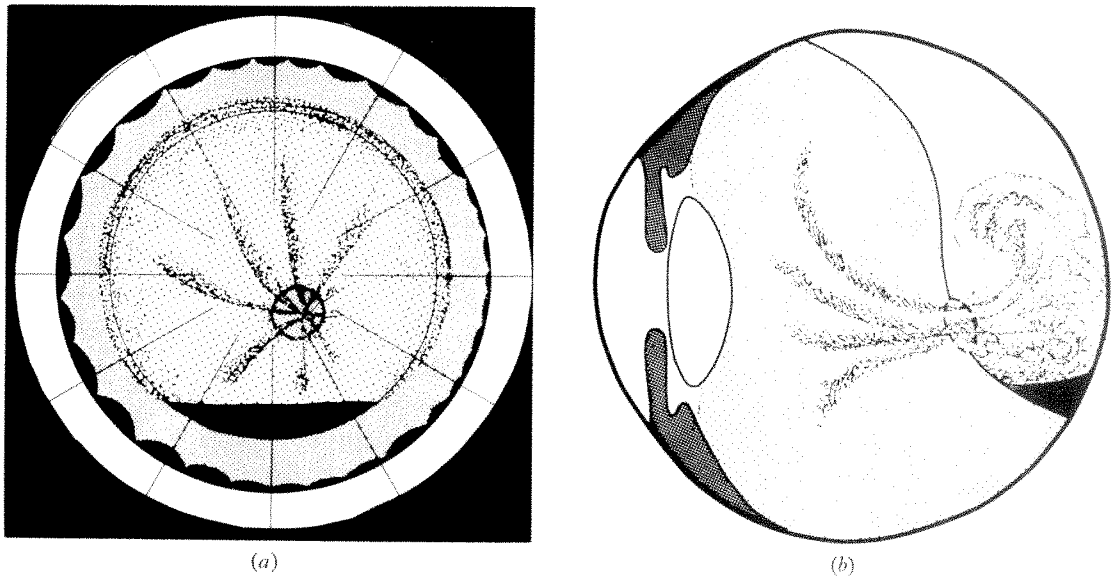
One hundred consecutive patients with acute vitreous haemorrhage who were treated with binocular occlusion and elevation from 1966 to 1974 at the New York Hospital were analysed. Forty-three were of rhegmatogenous origin and 57 bled from haemorrhagic vasculopathies (Table I). Eighty-two of the 100 patients were hospitalized. Eighteen diabetics, 15 of whom were recurrent bleeders, were treated as outpatients. All patients had both eyes covered. They spent most of their waking hours sitting in a chair where they were also fed. The dietetics department devised a menu of

Address for reprints: Harvey Lincoff, MD, 440 E. 57th Street, New York, New York 10022, USA



(*a*) (*b*)

FIG. 2 *Acute retinal haemorrhage confined by hyaloid membrane to posterior hyaloid space.* (a) *Blood cells have settled to bottom of space in* 14 *hours to reveal retinal tear at* 11 *o'clock.* (b) *Sagittal section. Some cells still on external surface of hyaloid membrane and in aqueous fluid below*



(*a*) (*b*)

FIG. 3 *Prolapse of vitreous through hole in posterior hyaloid membrane.* (a) *Red cells dispersing into gel along membranelles.* (b) *Sagittal section shows vitreous gel in posterior hyaloid space*

finger foods consisting of sandwiches, raw vegetables and fruits, and other foods that required a minimum of aid. Sleeping with the head of the bed raised 30 degrees was found adequate to encourage and maintain pooling of the blood at the bottom of the eye. Mobilization for toilet and for walking in the corridor had no dispersing effect as long as patching was maintained. A few minutes of unpatching a day for washing and examination did not provoke significant mixing. Pinhole glasses retarded dispersion but did not prevent it.

Inpatients were examined daily, outpatients every second or third day. Patches were maintained if there was perceptible clearing at each examination. Clearing time for the purpose of this report is defined as the day the retina could be seen well enough for diagnosis. Treatment consisted of cryopexy to retinal tears,

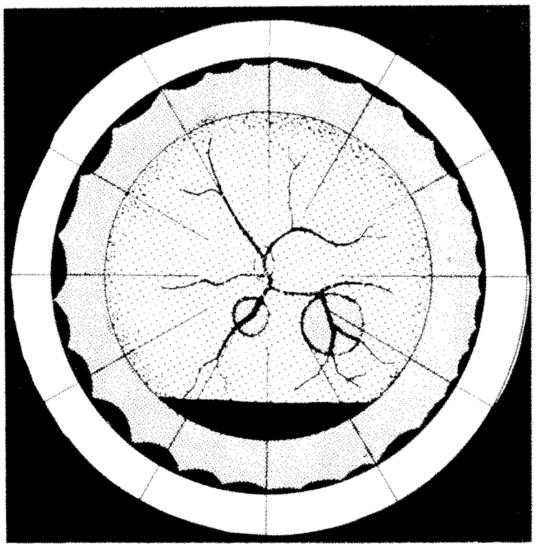


FIG. 4 *Two round holes in posterior hyaloid that appeared on second day after acute vitreous detachment and haemorrhage. Blood has collected below as a result of occlusion and elevation*

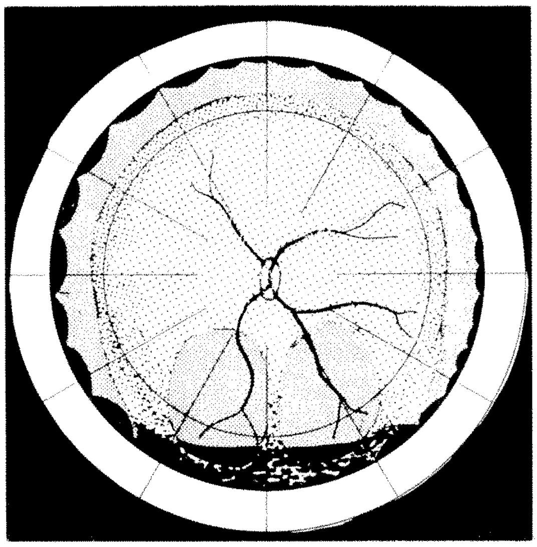


FIG. 5 *Holes in posterior hyaloid have expanded to bottom of eye. Blood is still collected below but has spilled over the surface of ciliary body*

scleral buckling for retinal detachment, and photocoagulation for the vasculopathies.

Results

RHEGMATOGENOUS HAEMORRHAGE

In none of the 43 patients with acute vitreous haemorrhage of rhegmatogenous origin was there evidence of a haemorrhagic vasculopathy in the second eye. These patients were treated with binocular occlusion with the expectation of finding a retinal break. Thirty-eight cleared—20 in one day, another 15 by four days, and three more by the end of a week (Table II). Acute retinal breaks were found in 25 cases, of which 16 were combined with retinal detachment. Four patients bled from bridging vessels across an operculated break that had been treated previously with cryopexy and scleral buckling. Nine patients had a posterior hyaloid detachment but no retinal break was found, and they were presumed to have bled from traction of the hyaloid on a retinal vessel.

Of the five patients in whom occlusion was abandoned because blood became diffuse in the gel two cleared over several months and were found to be without retinal breaks. Three did not clear before they showed signs of retinal detachment. One occurred in a woman aged 93 years, before the advent of ultrasound. The vitreous did not clear in the remaining four years of her life, but since she lost perception of light during this time she was presumed to have a retinal detachment. A second was a patient with a recent aphakia who reported,

Table I *Results of ocular immobilization of 100 consecutive patients with acute vitreous haemorrhage*

Aetiology	*No.*	*Cleared*	*Not cleared*
Rhegmatogenous	43	38	5
Bleeding vasculopathies			
Diabetes	50	45	5
Vein occlusion	5	4	1
Sickle cell	1	1	0
Leber's miliary aneurysms	1	1	0
Total	100	89	11

Table II *Clearing time of 38 cases of rhegmatogenous vitreous haemorrhage that responded to ocular immobilization*

Aetiology	*No.*	*Clearing time (days)*		
		1	2–4	5–7
Retinal tears	9	7	2	—
Tears with detachment	16	9	6	1
Bridging vessel on scleral buckle	4	2	1	1
Posterior hyaloid detachment without tear	9	2	6	1
Total	38	20	15	3

six weeks after his haemorrhage, a rising horizontal opacity superimposed on his vitreous density. Ultrasound confirmed the presence of a retinal detachment. A pars plana vitrectomy was done in combination with retinal detachment procedure. The retina reattached and vision recovered to 20/40. The third patient with a very dense haemorrhage had not cleared after 22 months. She had developed a defective light field and ultrasonography showed a retinal detachment. She refused surgical intervention.

BLEEDING VASCULOPATHIES (Table III)

Diabetic

Fifty patients who were treated with occlusion had bled from retinopathy of diabetic origin. All had diabetic retinopathy in the other eye. Out of the 50, 45 cleared—seven in one day, 19 by four days, and 11 by seven days. Occlusion was sustained in six patients for one to 28 days and in two patients for one to three months in order to obtain clearing of a slightly hazy gel and to prevent a larger amount of blood that had collected at the bottom of the retrohyaloid space from also entering the gel. Twenty-nine patients had a history of previous haemorrhage into the vitreous. This proved not to affect clearing time; recurrent bleeders cleared as quickly as initial ones. In diabetics the posterior hyaloid membrane seems more resistant to hole formation. Tolentino, Lee, and Schepens (1966) reported holes in 10 out of 40 diabetic eyes that bled.

VENOUS OCCLUSION

Five patients without haemorrhagic vasculopathy in the other eye were treated for vitreous haemorrhage with occlusion and elevation. All had hypertension, but the pertinent common factor was a history of branch vein occlusion in the bleeding eye 10–22 months previously. Four of the five cleared by day five and proved to have bled from secondary neovascularization in the occluded zone.

Table III *Clearing time of 51 cases of bleeding vasculopathy that responded to ocular immobilization*

Aetiology	*No.*	*Clearing time (days)*				
		1	2–4	5–7	8–28	>28
Diabetes	45	7	19	11	6	2
First haemorrhage	(16)	(3)	(8)	(2)	(2)	(1)
Recurrent haemorrhage	(29)	(4)	(11)	(9)	(4)	(2)
Vein occlusion	4	1	2	1	0	0
Sickle cell	1	0	1	0	0	0
Leber's miliary aneurysms	1	1	0	0	0	0
Total	51	9	22	12	6	2

Sickle-cell disease

One patient bled from the vascular malformations of sickle-cell disease and had sickle-cell vasculopathy in the other eye. The eye cleared sufficiently for photocoagulation in three days.

Leber's miliary aneurysms

A single patient with Leber's disease cleared in one day. There was typical vasculopathy in the other eye.

Discussion

Acute intraocular haemorrhage in the absence of diabetic haemorrhagic retinopathy or haemorrhagic retinopathy of other systemic origin in the other eye is most likely to be the result of a retinal tear (Lincoff, 1967; Lincoff and Kreissig, 1975). Morse, Aminlari, and Scheie (1974) collected 200 cases of spontaneous vitreous haemorrhage. Analysing these it is evident that if only the diabetics (108) are excluded 76 per cent (69 of 92) of idiopathic vitreous haemorrhages were of rhegmatogenous origin. In our series, excluding patients with diabetic vasculopathy in the other eye, 86 per cent (43 of 50) of idiopathic haemorrhages were of rhegmatogenous origin. This would seem to justify emergency management of at least this group of patients with vitreous haemorrhage and to discourage the practice of sending them first for diabetic or hypertensive treatment.

Bleeding of diabetic origin in a patient without diabetic changes in the second eye did not occur in our series. Nor did we see vitreous haemorrhage due only to hypertension. The five hypertensives in the series all bled from secondary neovascularization and had a history of retinal vein occlusion. Delay in instituting ocular immobilization and positioning of the patient increases the likelihood of holes developing in the posterior hyaloid membrane and blood entering the gel, resulting in prolonged obscuration of the fundus.

Summary

In the first hours after a vitreous haemorrhage dense enough to obscure the retina, the blood is usually confined to the posthyaloid space in an aqueous

phase. Binocular occlusion and elevation provides sufficient immobilization of the eyes in nine out of 10 patients for the blood cells to settle to the bottom of the space and make the retina available for examination and repair. Blood enters the vitreous gel through holes that develop in the posterior hyaloid membrane. Blood in the gel does not settle and requires months to clear.

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Diabetic retinopathy with normal glucose tolerance

A. D. B. HARROWER AND B. F. CLARKE
From the Diabetic and Dietetic Outpatient Department, Royal Infirmary, Edinburgh

Various histological (Siperstein, Norton, Unger, and Madison, 1966; Siperstein, Unger, and Madison, 1968; Siperstein, Unger, and Madison, 1970) biochemical (Camerini-Davalos and Cole, 1970; Goto, Toyota, Takaku, Sato, and Irie, 1970), growth hormone (Soeldner, Sönksen, Gleason, and Boden, 1971) and insulin secretory (Cerasi and Luft, 1967) abnormalities have been reported in 'pre-diabetics' who, by definition, have normal standard glucose tolerance. Despite this, however, there have been only a few reports of typical diabetic complications, particularly retinal (Collens, Silverstein, and Dobkin, 1959; Levine, 1961; Linner, Svandborg, and Zelander, 1965; Johansen, 1969; Siperstein, 1969) or renal (Collens and others, 1959; Linner and others, 1965) angiopathy occurring in such subjects.

A patient who presented with typical diabetic exudative and proliferative retinopathy, but had normal standard glucose tolerance, is described. It was concluded that in such cases the diabetes was probably latent, the retinopathy being discovered during a period of natural or induced remission when glucose tolerance had reverted to normal.

Case report

A 62-year-old woman was referred by her family doctor because of visual impairment which had developed gradually during the previous year. There had been no previous hospital admissions and apart from her presenting complaint she was asymptomatic. She had been obese since her teens, had not been known to be hypertensive, nor at any time in the past had she noted symptoms suggestive of diabetes mellitus. An older sister aged 71 years was a known maturity-onset diabetic attending the same clinic; she had been registered blind as a result of progressive exudative and proliferative diabetic retinopathy which had been present at diagnosis 10 years previously.

On examination, the patient was markedly obese, weighing 86·5 kg (standard weight 61 kg). She was hypertensive, with blood pressure 190/110 mmHg, but her general physical examination was otherwise unremarkable. The visual acuity was reduced to 6/18 in the right eye and 6/36 in the left. Ophthalmoscopy revealed features characteristic of diabetic retinopathy with scattered microaneurysms and small discrete round 'blob' haemorrhages (particularly in the posterior polar regions of both retinae) and extensive clusters of yellowish, deep, hard exudates in the macular and perimacular regions. In addition, there was vitreous haze with a few small areas of neovascularization along the superior and inferior temporal vessels in the right eye and, in the left, a few areas of early neovascularization in relation to the superior temporal veins. There was also mild arterio-venous 'nipping' and a few superficial linear haemorrhages compatible with the hypertension. Unfortunately, because of vitreous haze it was not possible to take satisfactory photographs.

Laboratory investigations showed a normal two-hour postprandial blood glucose of 4·1 mmol/l (74 mg/100 ml) and full blood investigation—including haematology, blood urea, electrolytes, and uric acid—were all normal. Urine microscopy was normal and renal function satisfactory, there being no proteinuria, the creatinine clearances were 68 and 115 ml/min and the intravenous-pyelogram was normal. Chest radiology showed slight cardiac enlargement affecting the left ventricle, but the electrocardiogram was normal. Urinary vanillyl mandelic acid was normal and the urinary 17-hydroxy-corticosteroid excretion was 20 mmol/day. Total plasma proteins were 73 g/l, albumin 40 g/l with a normal electrophoretic pattern. Immunoelectrophoresis of the globulins was normal, and tests for antinuclear factor were negative. Fasting cholesterol was 7 mmol/l, triglycerides 147 mmol/l, and free fatty acids 1050 mmol/l; a full clotting screen was normal. The standard oral glucose tolerance test, using a 50 g glucose load, which was repeated after an interval of seven days were both normal apart from a slight increase in the one-hour blood glucose value in the second test (Table I). Intravenous tolbutamide (Unger and Madison, 1958), and cortisone augmented glucose tolerance tests (Fajans and Conn, 1954) were likewise normal (Table I).

A renal biopsy showed, on light microscopy, hyaline changes in the arterioles compatible with hypertension, but, unfortunately the tissue obtained was inadequate for a satisfactory assessment of diabetes.

The hypertension was controlled with debrisoquine 45 mg daily and treatment was begun with clofibrate, 2·0 g daily, for the exudative element of the retinopathy (Duncan, Cullen, Ireland, Nolan, Clarke, and Oliver, 1968; Cullen, Town, and Campbell, 1974). During the subsequent three years there were vitreous haemorrhages in both eyes, and three years later the patient's visual acuity was reduced to counting fingers in the

Address for reprints: A. D. B. Harrower, MRCP, Diabetic and Dietetic Outpatient Department, Royal Infirmary, Edinburgh

Table I *Blood glucose mmol/l (mg/100 ml) during tolerance tests of oral glucose, cortisone-augmented glucose, and tolbutamide*

Oral glucose tolerance test (mmol/l (mg/100 ml))	*Time (hours)*						
	F	½	1	1½	2	2½	3
Test 1	5·0 (90)	9·7 (175)	7·7 (138)	3·8 (68)	2·7 (48)	—	—
2	4·9 (88)	8·4 (152)	11·4 (206)	8·1 (146)	5·3 (96)	4·0 (72)	2·7 (48)
Cortisone-augmented glucose tolerance test							
Test 1	5·9 (106)	11·3 (203)	10·8 (194)	7·7 (138)	4·7 (85)	4·0 (72)	2·7 (48)
2	6·4 (115)	12·5 (225)	11·1 (200)	5·1 (92)	5·1 (92)	—	—
Tolbutamide tolerance test	*Time (minutes)*						
	F	20	30				
	5·0 (90)	3·6 (65)	3·1 (55)				
Percentage decrease in blood glucose		28	38				

right eye but remained at 6/36 in the left despite two further vitreous haemorrhages. The Figure shows the current retinal appearances in the right eye with microaneurysms, haemorrhages, extensive hard exudates, and fibrosis. There had been a further vitreous haemorrhage in the left eye making photography impossible. The standing blood pressure is 200/100—180/90 mmHg and her weight has decreased by 12 kg. Random fasting and postprandial blood glucose values have been checked frequently and have remained well within the normal limits (range 3·6–5·8 mmol/l) (65–104 mg/100 ml) during this period and a repeated cortisone glucose tolerance test was similar to that obtained originally (Table I).

Discussion

There is a paucity of reports of typical diabetic retinopathy in patients with normal glucose tolerance (Table II) which might be expected to occur more commonly if biochemical and histological abnormalities precede glucose intolerance as has been frequently observed (Siperstein and others, 1966, 1968, 1970; Cerasi and Luft, 1967; Camerini-Davalos and Cole, 1970; Goto and others, 1970; Soeldner and others, 1971).

Typical diabetic retinopathy at the time of diagnosis is, however, well recognized and has been variously reported as occurring in 4 to 15 per cent of patients (Waite and Beatham, 1935; Lawrence, 1951; Aarseth, 1953; Lundbaek, 1955; Kornerup, 1958; Pyke and Roberts, 1959; Soler, Fitzgerald, Malins, and Summers, 1969). In such cases the diabetes has probably been long standing and undiagnosed because of the mildness or absence of symptoms. Indeed, it has been calculated that for persons diagnosed over the age of 50 years, the mean length of time between the appearance of impaired carbohydrate tolerance and diagnosis is at least 10 years (Anderson, 1966).

There have been reports of minimal capillary basement membrane changes in various tissues such as ear lobe (Camerini-Davalos, 1965) and muscle (Siperstein and others, 1966, 1968, 1970) in 'pre-diabetics'. The demonstration of impaired insulin release in the close relatives of diabetics who have normal standard glucose tolerance (Cerasi and Luft, 1967), suggests that biochemical abnormalities may be present for some time before the development of overt diabetes and it is possible that the basement membrane changes are secondary to these. However, Bloodworth, Engerman, Camerini-Davalos, and Powers (1970) also using thigh muscle biopsies found no difference between the capillary basement membrane thicknesses in 'pre-diabetics' and their controls. Østerby (1970, 1972) failed to demonstrate significant basement membrane thickening in glomerular capillaries from recently diagnosed young diabetics, in whom the date of onset of diabetes could accurately be obtained. By studying successive renal biopsies during the next 2½ years, however, she showed a progressive increase in basement membrane thickness.

The patient we describe had a retinopathy which showed the typical combination and distribution of features characteristic of diabetes and with no evidence of veno-occlusive disease, hyperviscosity syndromes, retinal vasculopathies, or other conditions known to produce changes which may resemble diabetic retinopathy. The fact that a sister, with confirmed diabetes, had similar retinal changes at diagnosis may indicate an enhanced familial predisposition to diabetic retinopathy. In such cases the patients are probably latent diabetics,

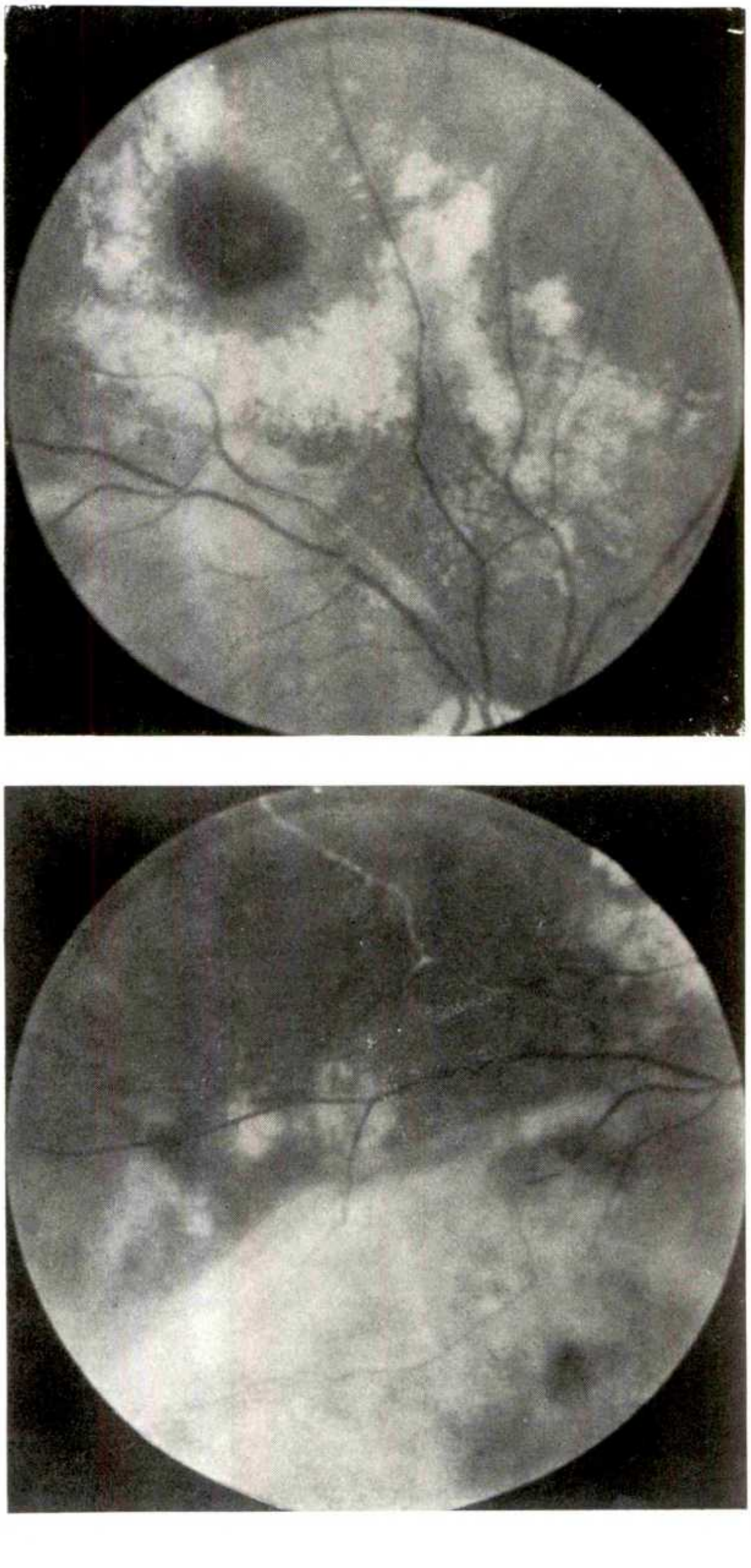

FIGURE *Retinal photographs showing microaneurysms, haemorrhages, hard exudates, and fibrosis in the right eye*

Table II *Reports of patients with normal glucose tolerance and typical diabetic retinopathy*

Reference	*Sex*	*Age*	*FH of diabetes*	*Retinal appearance*	*Other angiopathy*	*Comments*
Collens and others, (1959)	Male	42	Yes	Hard exudates, microaneurysms, haemorrhages	Nodular glomerulosclerosis	Obese. BP 180/100. Diabetes diagnosed 17 years before, but GTT normal at time of report. Abnormal cortisone-augmented GTT
Levine (1961)	Female	'early forties'	?	Haemorrhages proliferation	—	8 GTT ± cortisol. 1 abnormal
Linner and others, (1965)	Female	60	Yes	Microaneurysms and dot haemorrhage, small hard exudates	No typical diabetic features on renal biopsy	Normotensive
Johansen (1969)	Male	65	Yes	Microaneurysms blob haemorrhages and new vessels	Diffuse glomerulosclerosis	Diabetes diagnosed 5 years before when patient obese. GTT normal, but became abnormal after weight gain
Siperstein (1969)	Female	54	Yes	Microaneurysms and haemorrhages	Quadriceps muscle biopsy showed increased capillary basement membrane thickness	GTT normal on repeated testing
Present case	Female	62	Yes	Microaneurysms and blob haemorrhages hard exudates, new vessels	—	Obese. BP 190/110

in whom retinopathy has been discovered during a period of natural or induced remission when standard glucose tolerance has reverted to normal. In the patient described genetic predisposition, the exacerbating effect of hypertension (Kornerup, 1958; Hollenhorst, 1962; Field, 1970), and insulin resistance caused by obesity may have been contributory factors.

Summary

A case is reported of a patient with typical diabetic retinopathy, but with normal glucose tolerance. Previously reported cases are reviewed and it is concluded that in such patients the diabetes is probably latent, the retinopathy being discovered during a period of natural or induced remission.

We are grateful to Dr L. J. P. Duncan for permission to study this present case and for his advice and criticism.

Dr J. F. Cullen was helpful in the assessment and management of the retinal changes and Dr D. Thomson and Dr J. T. Ireland advised us on the renal biopsy material.

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Corneal neovascularization treated with argon laser

PAUL M. H. CHERRY[1] AND ALEC GARNER[2]
From the Pocklington Eye Transplantation Research Unit, Toronto[1], and the Pathology Department, Institute of Ophthalmology, London[2]

Corneal neovascularization can be troublesome, especially in an eye which is to have a corneal graft. A corneal transplant is more likely to be rejected in a vascularized than a non-vascularized cornea. In this and many other clinical situations, therefore, it is desirable that corneal new vessels be obliterated. Many treatments have been suggested, including corticosteroids, irradiation, thiotepa, cryotherapy, photocoagulation, cysteine, chondroitin sulphuric acid, and dextran. One of us (PMHC) was, we believe, the first to report the use of the argon laser in the treatment of corneal neovascularization in man (Cherry, Faulkner, Shaver, Wise, and Witter, 1973). This was an open trial in four patients, two with chemical burns of the cornea and two with herpes simplex keratitis. There were two failures, one success, and one partial success. It was impossible to draw any definite conclusions from so few cases, and it was therefore decided to embark on a controlled trial in rabbits.

Materials and methods

One of the eyes of each of 11 pigmented Dutch rabbits were used as both case and control. Each animal weighed about 2 kg. Two 7′ 0′ or 8′ 0′ black silk sutures were placed in the cornea about 3 mm in from the limbus, one at 10 o'clock and one at 2 o'clock. The animals were anaesthetized with intravenous sodium pentobarbitone. Usually the cornea was perforated during suture placement with slight resultant loss of aqueous and shallowing of the anterior chamber. In every case the chamber quickly re-formed and no anterior synechiae to the corneal perforation ensued. The sutures were used as the stimulus for corneal new vessel formation, which took about three weeks to reach the sutures from the limbus. When neovascularization was adequate the sutures were removed. Corneal fluorescein angiograms were then obtained under anaesthesia to document accurately the position of the vessels and determine which were arteries and which were veins. A modified Zeiss photoslit lamp camera was used for the angiography with a Balzar interference excitation filter (FITC 4) and a Kodak Wratten 15 barrier filter.

Because of the positioning of the sutures two sectors of vessels were stimulated, one from the upper nasal limbus and the other from the upper temporal limbus. Two sectors of vessels in the same eye were needed so that one could be used as a control and the other as the argon-treated area. The argon laser therapy was performed under sodium pentobarbitone anaesthesia and repeated at intervals of several days until the vessels were completely occluded. (Only one animal, no. 2, was killed before the treated vessels were occluded. This was done deliberately to obtain some histological specimens very soon after argon laser treatment.)

The technique of laser therapy was as follows. Both arteries and veins were treated as they crossed the limbus and 2 to 3 mm to the corneal side of the limbus. The first treatment of each vessel was 'downstream' and the second 'upstream', thus trapping a column of blood which was able to absorb subsequent treatment of the vessel between these two points. Intravenous fluorescein was usually given immediately before the argon laser therapy so that more laser energy would be absorbed by the corneal vessels as they were being treated (Kohner, personal communication). Intravenous fluorescein was repeated during the treatment session to document the success or failure of each stage of the treatment. When the treated sector of corneal vessels was occluded the fluorescein angiograms were repeated at intervals of several days to make sure that the control vessels were still patent. The iris damage during the experiment was also documented with fluorescein angiography until the changes were stabilized. The instrument used for the argon laser therapy was manufactured by Coherent Radiation, Palo Alto, California, USA. The settings were usually 50 μm spot size, 0·2 s exposure time, and 150 mW energy (see Table).

When the animals were killed their treated eyes were enucleated for histopathological study. Just before some of the animals were killed the pupil of the treated eye was dilated and the fundus examined with the indirect ophthalmoscope to determine if there was any visible retinal damage. No damage was found.

Results

The results are summarized in the Table. The argon laser was effective in obliterating corneal new vessels, provided a continued stimulus for revascularization of the cornea was not present. An active stromal infiltrate in the area of the suture

Address for reprints: Paul M. H. Cherry, FRCS, Department of Ophthalmology, University of Toronto, 1 Spadina Crescent, Toronto, Canada

Table *Results of Argon laser treatment of corneal neovascularization in 11 pigmented Dutch rabbits*

Rabbit no.	*Sutures removed on day:*	*Argon laser treatment on days:*	*No. of treatments*	*No. of shots at each treatment*	*Power setting (mW)*	*Animal killed on day:*	*Control vessels patent at death of animal*	*Eye*	*Nasal or temporal vessel sector treated*
1	0	9, 10, 13, 14	4	230 134 150 226 740	272 at 100 92 at 200 150 at 250 226 at 300 740	164	No (gone by day 132)	Right	Temporal
2*	0	16	1	350	200	20	Yes	Left	Temporal
3	0	0, 3, 10, 13, 17, 42	6	745 471 382 586 291 394 2869	2283 at 150 586 at 250 2869	80	No (gone by day 69)	Left	Nasal
4	0	0, 7, 10	3	375 99 312 786	150	77	Yes	Right	Nasal
5	0	11, 21	2	467 280 747	150	91	Yes	Left	Nasal
6	0	3, 7, 14	3	368 451 320 1139	150	25	Yes	Right	Temporal
7	0	0, 7	2	88 194 282	150	18	No (gone by day 14)	Left	Temporal
8	0	0, 4, 28	3	2299 1456 567 4322	100	32	Yes	Right	Temporal
9	0	7, 14, 18	3	482 307 239 1028	987 at 150 41 at 250 1028†	63	Yes	Left	Nasal
10	0	3, 7, 14	3	249 415 316 980	664 at 150 316 at 200 980	25	Yes	Left	Temporal
11	0	3, 8	2	833 288 1121	150	46	Yes	Right	Nasal

*Rabbit deliberately killed before occlusion to study histopathology very soon after argon laser treatment

†Forty-one burns were at 100 μm spot size not 50 μm

scar was apparent during the sessions of argon laser therapy in rabbits 3 and 8, and these were the two animals which required the greatest number of laser shots (2869 and 4322 at six and three treatment sessions respectively). In both these animals, however, the laser-treated sector was successfully occluded after the suture scar inflammation had resolved.

When occluding the vessels an effort was made to use the minimum amount of argon laser energy possible, thus limiting the iris damage. The minimum spot size (50 μm) was used (except for 41 shots of 100 μm spot size in rabbit 9) together with an exposure time of 0·2 s: 150 mW of energy was usually selected, but 100, 200, 250, and 300 mW were occasionally used. Rabbit 8 had only 100 mW treatment, and we suggest that this power meter setting is adequate so long as no stimulus for revascularization of the cornea remains.

We hoped that it would be enough to treat only the arteries and that the veins, deprived of their blood supply, would then spontaneously regress. But this was not found to be the case in rabbit 11 (Figs 1–5), in which all arteries in the treated sector were successfully obliterated by day 3 after suture removal; the veins were not treated. However, when examined on day 8 the vein marked V_2 was carrying blood to the suture scar from the limbus and had thus become the afferent part of a venous loop. V_2 was obliterated with the argon laser on day 8. The rabbit was next seen on day 11, when V_3 was the afferent limb of a venous loop and V_1 the efferent limb (Fig. 5). By this time the vessels were of very fine calibre and V_3 and V_1 spontaneously disappeared by day 14. Thus, two examples of retrograde flow were demonstrated in this rabbit, and it is therefore not sufficient to treat only arteries when attempting to obliterate corneal new vessels.

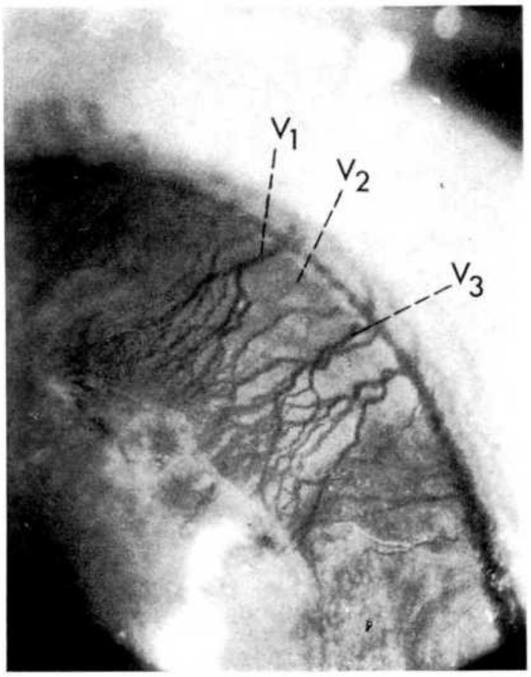


FIG. 1 *Rabbit 11. Pretreatment photograph of 2 o'clock sector of vessels.* V_1, V_2, *and* V_3 *are veins*

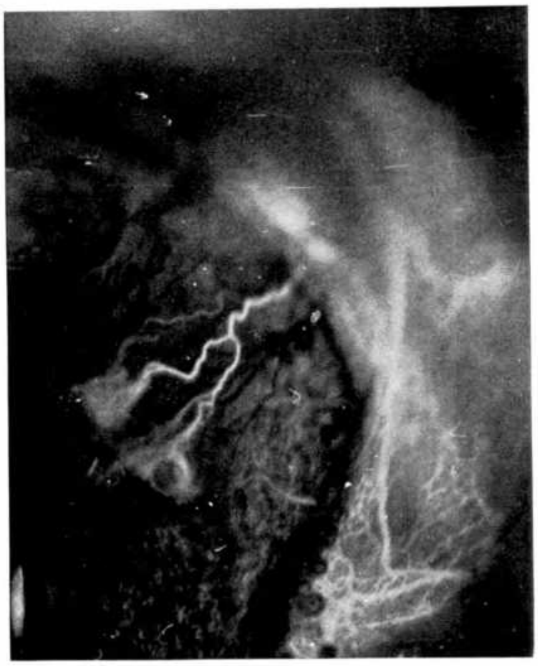


FIG. 2 *Rabbit 11. Pretreatment fluorescein angiogram, right eye, showing 2 o'clock sector of vessels in arterial phase*

Before each session of argon laser therapy fluorescein was given intravenously to ensure that maximum laser energy would be taken up by the corneal blood vessels (Kohner, personal communication). The smaller and less obvious vessels could also be visualized and therefore treated. Additionally, fluorescein given intravenously several times during each treatment helped to show when the vessels had been occluded.

Apart from in rabbit 2, the laser therapy eventually closed all the treated sectors of vessels. This rabbit was purposely killed four days after the first and only session of laser therapy in order that histopathology of the acute lesion might be observed. In the remaining 10 rabbits the average number of treatment sessions required to obliterate the vessels was 3·1. The animals were then observed for varying periods before being killed to make sure that the control vessels remained patent and did not disappear spontaneously. The control vessels in rabbits 1, 3, and 7 did disappear spontaneously at days 118, 27, and 7 respectively after successful occlusion of the treated vessels. The control vessels of the other rabbits remained patent until they were killed.

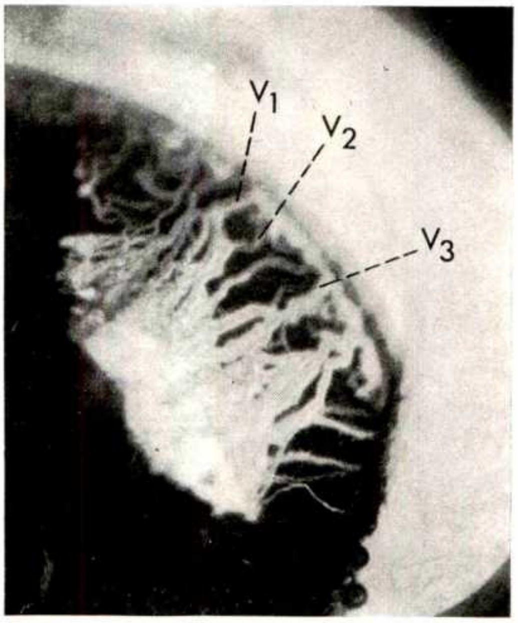


FIG. 3 *As for Fig. 2 showing 2 o'clock sector of vessels in venous phase.* V_1, V_2, *and* V_3 *are veins*

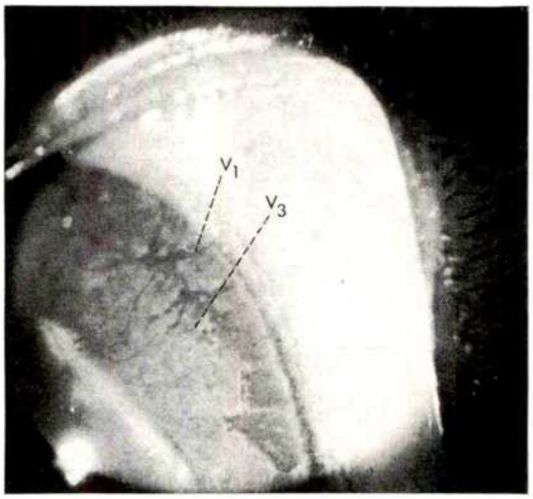


FIG. 4 *Rabbit 11. Photograph day 11 after argon laser treatment. Veins* V_1 *and* V_3 *are only vessels remaining patent*

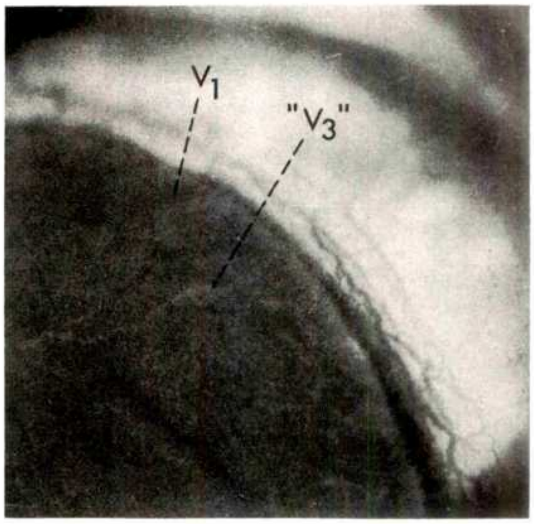


FIG. 5 *Rabbit 11. Fluorescein angiogram day 11 after argon laser treatment. "*V_3*" is afferent limb and* V_1 *efferent limb of a venous loop. "*V_3*" has filled from limbus and is beginning to empty into* V_1

Changes in the iris were observed at the time of laser application in all animals. Energy not absorbed by the corneal blood vessels reached the iris and caused a pigment disturbance on the surface. A black patch appeared on the surface of the iris underneath the treated vessel and sometimes the iris surface became slightly excavated, but by about two months the excavation was almost imperceptible and the hyperpigmentation of the black patch was less marked. In rabbit 1 these iris changes were accompanied by very slight ectropion uveae.

Fluorescein angiography was performed on the non-vascularized eye of rabbit 9 two to three hours after the application of 601 (108 mW, 50 μm, 0·2 s) argon laser burns to the iris (Figs 6–9). The black patches did not fluoresce, the pigment, acting as a curtain, preventing fluorescence from the underlying iris stromal vessels. Dots of fluorescein leakage, however, appeared from many iris vessels, including those at the edge of the black patches, within 30 seconds of intravenous fluorescein injection (Fig. 8), and these dots slowly increased in size. There was also a massive outpouring of aqueous from the ciliary body. Thirty to 60 seconds after intravenous fluorescein injection fluorescent aqueous started to enter the anterior chamber through the pupil, and after about five minutes the iris could hardly be seen in blue light because of the large amount of

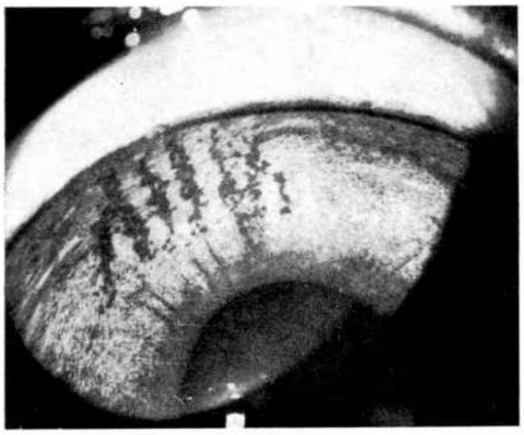


FIG. 6 *Rabbit 9. Photograph of right eye two to three hours after application of* 601 (100 *mW*, 50 μm, 0·2 *s*) *argon laser burns to iris (corneal vessels not induced in this eye). Note black patches of iris damage*

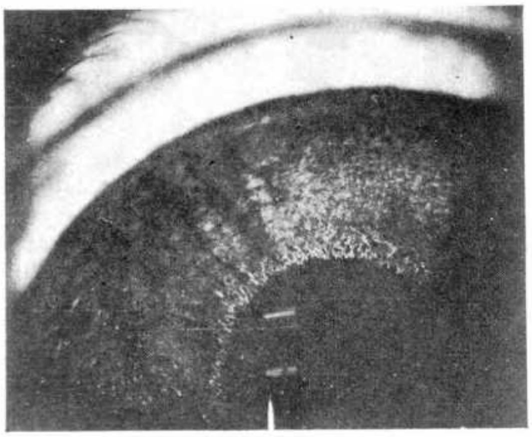


FIG. 7 *As for Fig. 6. Black patches of iris damage mask fluorescence* (15 *s post-injection*)

fluorescent aqueous in the anterior chamber. The rabbit's other eye was used for comparison and there the entry of fluorescent aqueous into the anterior chamber via the pupil was much less. Three days after the application of the laser the amount of aqueous produced by the ciliary body was much less, and a week after the laser treatment it had returned to normal (Fig. 10). The focal iris leakage seen two to three hours after treatment (Figs 8, 9) had ceased.

PATHOLOGY

The corneal blood vessels seen in histological sections were generally in the superficial stroma immediately beneath the epithelium, although in three animals (1, 4, and 7) vascularization was more obvious in the deep or midstroma. The vessels on the treated side of the cornea were variably surrounded by scanty macrophages, lymphocytes, and proliferated fibrous scar tissue. In most instances the vessel would appear to have been completely destroyed (Fig. 11*a*, *b*), while occasional less severely damaged vessels were occluded by thrombus. Two corneae (rabbits 8 and 10) showed small solitary aggregates of necrotic debris associated with trivial leucocytic infiltration between Descemet's membrane and the lining endothelium (Fig. 12). These probably represented the site of perforation into the anterior chamber of the sutures inserted into the cornea to induce vascular ingrowth.

Iris lesions were included in the sections of four eyes (rabbits 2, 8, 9 (right eye), and 11). In each case they presented as minute foci of stromal pigment disturbance which had given rise to tiny accumulations of melanin-laden macrophages near to the anterior surface of the iris (Fig. 11*c*). There was no sign of residual necrosis or inflammation, and the pigment epithelium on the posterior surface of the iris was intact in every instance.

Discussion

The power of the argon laser is confined to the green and blue regions of the spectrum with 80 per cent of the total confined to two wavelengths, 5145 Å (green) and 4880 Å (blue) (Campbell, Rittler, Swope, and Wallace, 1969). Energy at these wavelengths is transmitted by the optical system of the eye with relatively low absorption and therefore high efficiency (Meyer-Schwickerath,

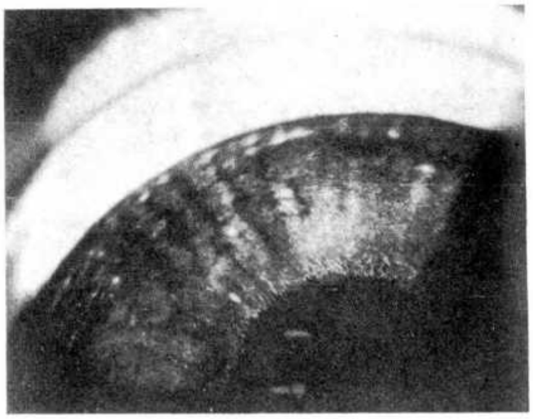


FIG. 8 *As for Fig. 6. Dots of fluorescein leakage from many iris vessels including those at edge of black patches* (30 *s post-injection*)

1960). Pigment epithelium absorbs a high degree of energy at these wavelengths, and a significant portion of the energy is also absorbed by blood (Geeraets, William, Chan, Ham, Guerry, and Schmidt, 1962).

The argon laser was effective in occluding suture-induced corneal new vessels, the sutures having been removed before treatment with the laser. In rabbits 3 and 8 an active infiltrate of the stromal suture scar remained after suture removal, and the argon laser did not occlude the vessels in these animals until the inflammation subsided. We therefore suggest that the argon laser can occlude corneal blood vessels in rabbits so long as there is no, or very little, stimulus remaining for revascularization. In these optimum circumstances very little laser energy has to be used to occlude the vessels (50 μm, 100–150 mW, 0·2 s).

The most obvious complication of argon laser therapy in these 11 Dutch rabbits was damage to the iris. This must particularly be borne in mind because of the iris route of corneal graft rejection (Jones, 1973). If the argon laser is to be used extensively to occlude corneal new vessels in man we think it will be to occlude corneal new vessels before keratoplasty. Therefore if argon laser therapy to corneal vessels is complicated by an increased chance of corneal graft rejection by the iris route it must surely be discarded as a means of treating corneal new vessels in these circumstances. Black iris patches, 'shadows' of the treated corneal vessels, appeared immediately on treating the vessels in our Dutch rabbits and were caused by any laser energy not taken up by the corneal vessels.

Unger, Perkins, and Bass (1974) showed that laser irradiation of the iris in pigmented Dutch rabbits is followed by a transient increase in intraocular pressure of up to 45 mmHg within 10 minutes, with a return to normal within 2 hours. They suggested that this increase is mediated by E-type prostaglandins. They also found a breakdown of the blood-aqueous barrier with increased permeability to plasma proteins occurring in the ciliary processes and not in the iris. Fluorescein angiography performed in our experiment confirmed the findings by Unger and others (1974). Angiograms two to three hours after the laser treatment showed no fluorescence through the surface black patches on the iris but there were focal dots of fluorescent leakage from many iris vessels, including those at the edge of the black patches (Figs 8, 9). This leakage persisted for a few days but had always resolved within a week. There was also massive outpouring of fluorescent aqueous from the ciliary processes, through the pupil, in the fluorescein angiograms two to three hours after laser treatment. The intraocular pressure was not measured at this time or immediately after laser treatment, but presumably it was transiently raised. The breakdown of the blood-aqueous barrier resolved slowly and was also back to normal within a week.

Histopathological examination of the iris lesions showed minute foci of stromal pigment disturbance which had given rise to tiny accumulations of melanin-laden macrophages near the anterior

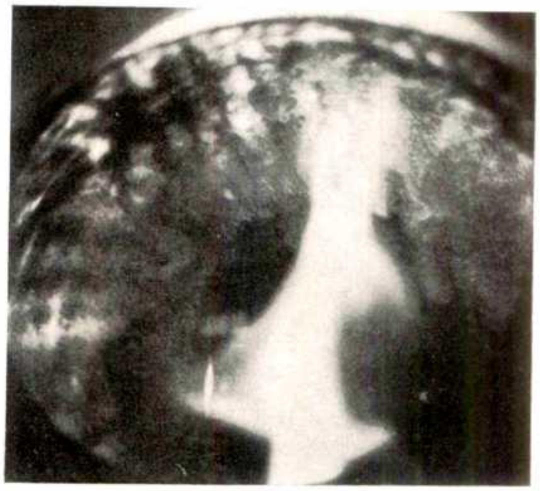


FIG. 9 *As for Fig. 6. Fluorescent aqueous beginning to pour into anterior chamber through pupil. Dots of fluorescein leakage from many iris vessels including those at edge of black patches. Black patches of iris damage mask fluorescence (45 s post-injection)*

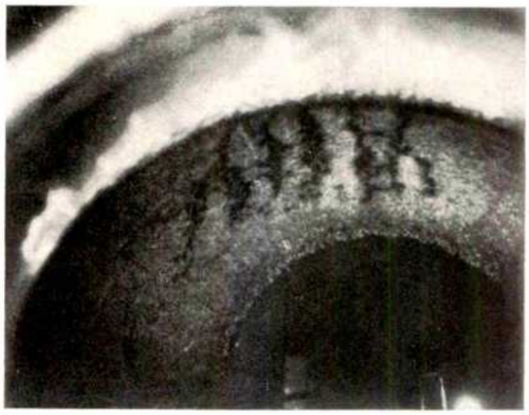
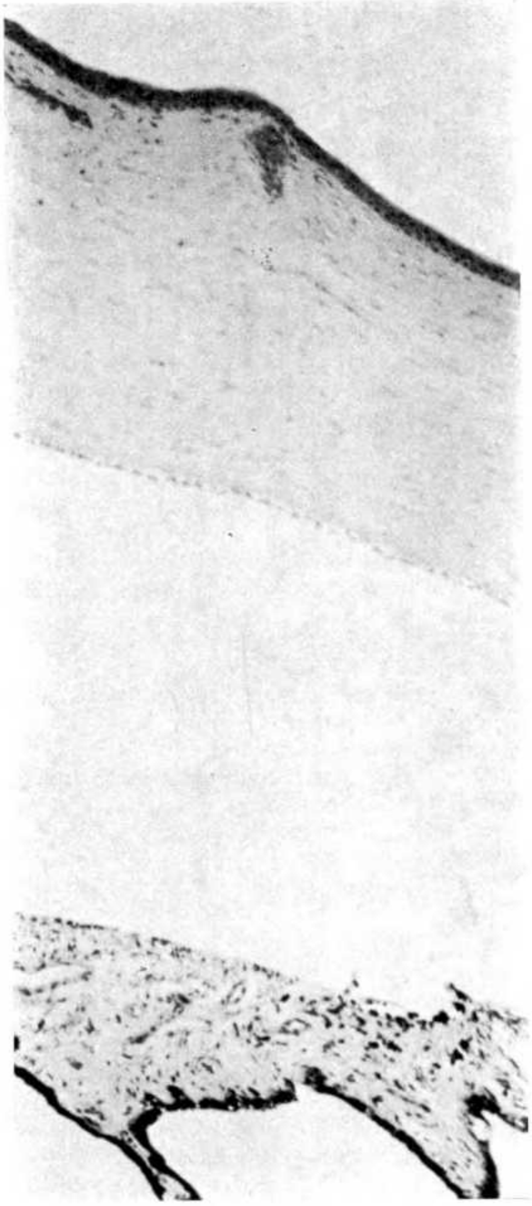


FIG. 10 *Rabbit 9. Fluorescein angiogram of right eye seven days after argon laser treatment to iris. Black patches of iris damage mask fluorescence. There is now no focal leakage of fluorescein from the iris vessels (about 1 min post-injection)*

surface of the iris (Fig. 11*c*). There was no sign of residual necrosis or inflammation and the pigment epithelium on the posterior surface of the iris was intact in every instance. This suggests that the iris damage stabilizes about one week after argon laser treatment of corneal blood vessels in pigmented Dutch rabbits and should not, therefore, necessarily contraindicate the use of the argon laser to treat corneal blood vessels in patients being considered for keratoplasty. The corneal vessels could be occluded about two weeks before the proposed keratoplasty, thus allowing the iris time to stabilize before the operation. It must also be mentioned that further work by Unger and Brown (personal communication) has shown, so far, that the blood-aqueous barrier in humans is much more stable after ruby laser therapy of the iris than that of pigmented Dutch rabbits.

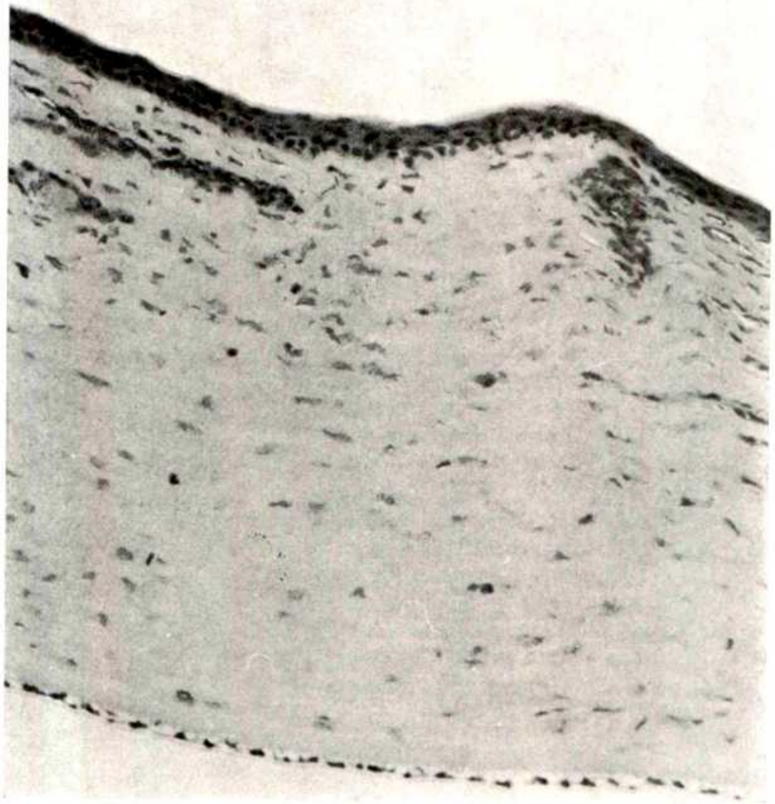
The following technique of argon laser treatment of corneal new vessels is recommended.

1. Suppress the corneal lesion which is stimulating the neovascularization with appropriate treatment, thus reducing the stimulus for revascularization to a minimum.
2. Perform intravenous fluorescein angiography at the time of laser therapy in order to determine which of the corneal vessels are arteries and which are veins and to visualize easily the smaller vessels. Furthermore, with fluorescein in the vessels at the time of laser therapy the energy absorption by the vessels is increased (Kohner, personal communication).
3. Set the argon laser at 100 mW, 50 μm, 0·2 s and treat the corneal arteries about 3 mm in from the limbus, and then 'upstream' at the limbus. Having isolated a column of blood in this manner, treat between these two points on all the arteries until the arteries are obviously occluded and the blood flow in the veins therefore stagnant. The laser power can be increased to 150 mW, but it should not be necessary to use a greater power.
4. The retrograde flow in the veins (Figs 2–5) is at first very sluggish, taking about a day to become fully established. Even then, the calibre of the venous loop vessels is always less than before the arteries were occluded. However, this retrograde flow makes it necessary to treat all vessels rather than just the arteries. The veins are first treated at the limbus, then 'upstream' 3 mm in from the limbus, and then between the two points just mentioned. They need far fewer laser shots than the arteries. They are treated immediately after the arteries, when the

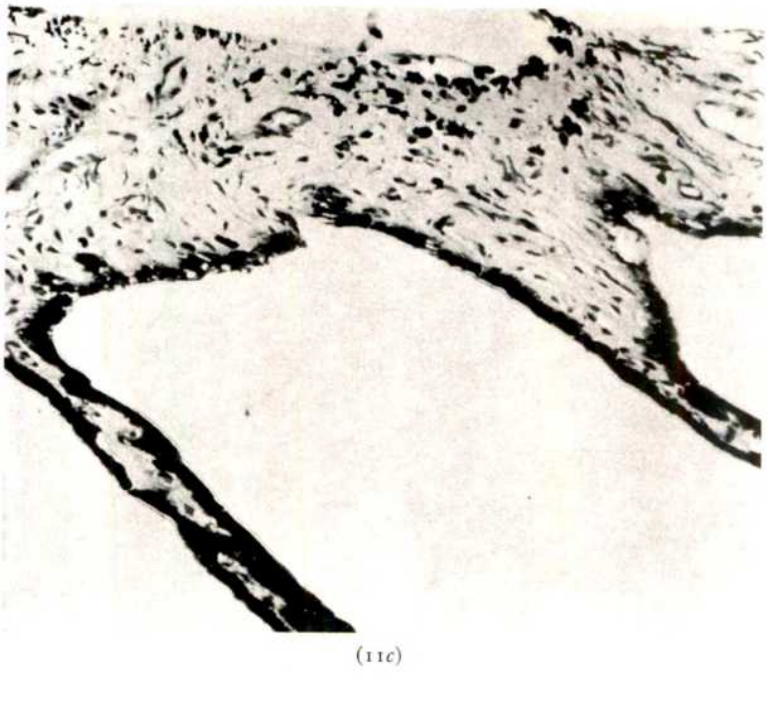


(11*a*)

FIG. 11 *Rabbit* 2. (a) *Section showing occluded blood vessel in superficial stroma of cornea associated with a little reactive scar tissue formation. Underlying iris shows small shallow excavation lined by pigment-filled macrophages: iris otherwise intact. Haematoxylin and eosin.* × 92. (b) *and* (c) *Higher magnifications of occluded corneal vessel and iris lesion seen in* (a). *Haematoxylin and eosin.* × 180



(11*b*)



(11*c*)

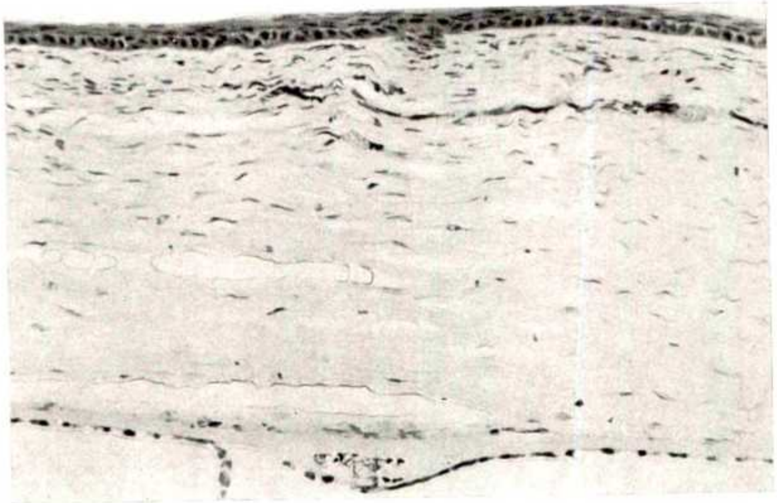


FIG. 12 *Rabbit 10. Several treated vessels in superficial corneal stroma associated with mild scarring; small focus of debris between Descemet's membrane and endothelium probably related to earlier insertion of silk suture to induce vascularization. Haematoxylin and eosin.* × 195

blood flow in the veins will be stagnant or very sluggish.

5. If retreatment of the vessels is necessary some days later it should be in a similar manner to the first treatment session, but fewer laser shots should be needed to occlude all corneal vessels at the second and any subsequent treatment sessions.

Summary

The argon laser set at 50 μm, 100–150 mW, 0·2 s occluded corneal blood vessels in pigmented Dutch rabbits provided the corneal lesion responsible for inducing vascularization was inactive. After arterial treatment with the argon laser retrograde flow in untreated veins was demonstrated by fluorescein angiography. Therefore all corneal new vessels should be treated, not just arteries. Minimal iris damage complicated the laser therapy, but this was not thought necessarily to contraindicate the use of the argon laser to treat corneal blood vessels in man. The iris damage was associated with outpouring of aqueous from the ciliary processes, and it took up to a week for the blood-aqueous barrier to return to its normal state.

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Spheroidal degeneration of cornea and conjunctiva

A. GARNER, F. T. FRAUNFELDER,* T. C. BARRAS, AND E. N. HINZPETER†
From the Department of Pathology, Institute of Ophthalmology,
University of London, and the External Disease Unit, Moorfields Eye Hospital, London

Small golden to yellow spherules in the cornea and conjunctiva have now been seen in people in every continent. There are, however, variations in the size, distribution, and number of the deposits, governed probably by environmental and nutritional factors, the duration of the condition, and the presence of other corneal lesions. Spheroidal deposits occurring in a band-shaped pattern across the central cornea are most common in regions in which the eyes are exposed to climatic extremes and the traumatic effects of wind-blown sand or ice (Bietti, Guerra, and Ferraris de Gaspare, 1955; Freedman, 1965; Freedman, 1973b; Rodger, 1973; Young and Finlay, 1975). In geographical areas subject to much sunlight but spared the traumatic effects of wind-blown sand or ice it is common to see other concomitant corneal or conjunctival lesions, particularly pingueculae (Klintworth, 1972; Fraunfelder and Hanna, 1973), while in countries blessed with little actinic radiation this may almost be the rule (Garner, 1970, 1972). The prevalence of spheroidal degeneration in temperate climes characterized by low levels of sunlight has, however, not been reported, and the purpose of this paper is to document its incidence in the cornea and conjunctiva as seen in an English eye hospital and to comment on its association with pinguecula.

Patients and methods

From January to July 1975 almost 1000 random patients seen in the outpatient clinic at Moorfields Eye Hospital, London, were examined using a slit lamp for the presence of corneal or conjunctival droplets (Fig. 1). Patients who had not spent at least three-quarters of their lives in Britain were excluded from the study. Photographs were taken using a macro camera (Brown 1970) and a Zeiss photoslit lamp.

Thirty-two eye bank eyes and five corneas known to contain spheroidal deposits were examined histologically, the tissue being fixed in formol saline and embedded in paraffin wax. Staining procedures included haematoxylin and eosin, Verhoeff-van Gieson, orcein, and Gomori's aldehyde fuchsin on untreated sections and sections predigested for six hours with pancreatic elastase (Fullmer, 1960).

Results

The prevalence of conjunctival and corneal spheroidal droplets at various ages is shown in Fig. 2. The overall prevalence was 6·5 per cent with a predominance of males in patients over 50 years old in the ratio of 7 men to 3 women. Droplets were four times more common in those who spent much of their time out of doors than in patients who lived predominantly indoors. Analysis of the deposits according to the criteria introduced by Fraunfelder and Hanna (1973) showed that each of the 62 affected patients had conjunctival droplets while 12 also had corneal droplets. There was no sign of previous lesions in any of these patients.

Histological study was directed primarily to the connexion between spheroidal droplets and the altered connective tissue fibres seen in the frequently associated pingueculae (Fig. 3). Nine of the eye bank eyes had conjunctival pingueculae and three of these also included spheroidal deposits. The coarse curled fibres of pingueculae stained with each of the elastic stains used, and whereas pretreatment with elastase had minimal effect on the subsequent response to Verhoeff's stain or Gomori's aldehyde fuchsin technique it usually prevented staining with orcein (Figs 4 to 6). The spheroidal droplets, on the other hand, failed to react with either orcein or aldehyde fuchsin irrespective of predigestion with elastase. Their positive response to Verhoeff's stain was also unaffected by elastase (Figs 7 to 9). The results are collated in Table I.

Discussion

EPIDEMIOLOGY

A comparison of the English data with the results of an American study in the State of Arkansas

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*Visiting Professor, Institute of Ophthalmology. Present address: Department of Ophthalmology, University of Arkansas Medical Center, 4301 West Markham, Little Rock, Arkansas 72201

†Visiting Worker, Institute of Ophthalmology. Present address: 2 Hamburg 20, Eisenlohrsweg 4, West Germany

Address for reprints: Dr A. Garner, Institute of Ophthalmology, Judd Street, London WC1H 9QS

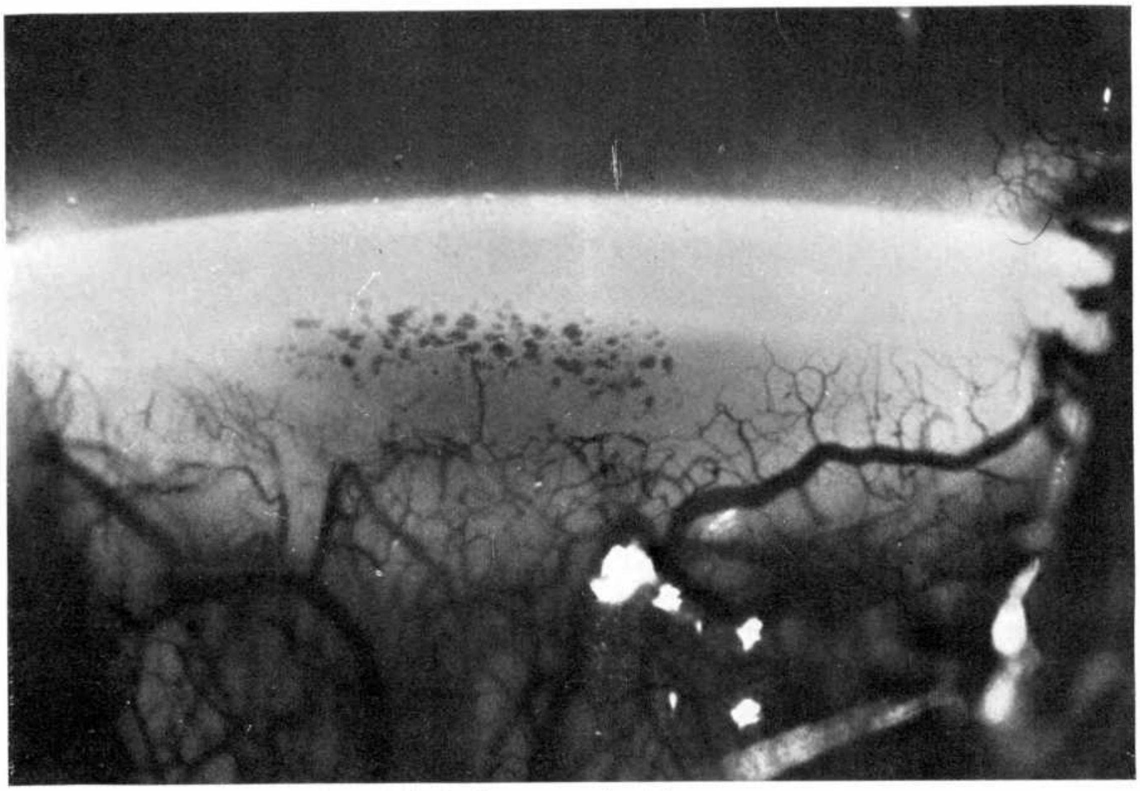


FIG. 1 *Clinical photograph showing multiple droplets at corneal periphery*

conducted according to the same criteria (Fraunfelder and Hanna, 1973) shows a considerable difference at all ages in the prevalence of spheroidal degeneration (Fig. 10). Of the environmental factors that were considered in the aetiology of the deposits only the amounts of actinic radiation in Arkansas and Britain are significantly different. This, together with the finding that a majority of the English patients with droplets spent much of their lives out of doors, supports the suggestion that exposure to sunlight is of pathogenic importance. Other geographical areas where the prevalence of spheroidal degeneration is high also have, among other things, much sunlight (Table II). Possibly the prevalence of the deposits in the general population in England is less than would seem from our data since our study was undertaken on outpatients to an eye hospital, who were therefore a selected group.

PATHOLOGY

Several workers have commented on the concomitance of spheroidal degeneration in the cornea and pinguecula (Klintworth, 1972; Fraunfelder and Hanna, 1973) and their similar staining properties (Brownstein, Rodrigues, Fine, and Albert, 1973; Rodrigues, Laibson, and Weinreb, 1975). Since apparently identical deposits have long been known to occur in the conjunctival tissue overlying pingueculae (Fuchs, 1891; Parsons, 1904; Hogan and Zimmerman, 1962; Klintworth, 1972) it has been proposed that both corneal and

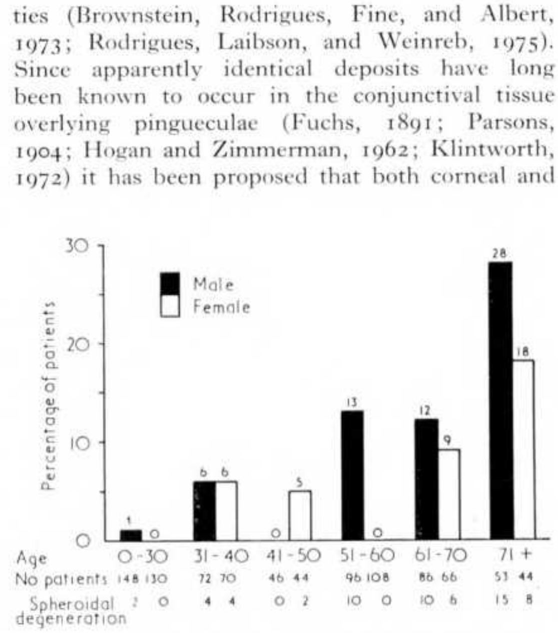


FIG. 2 *Prevalence of spheroidal droplets in conjunctiva and/or cornea in British subjects related to age and sex*

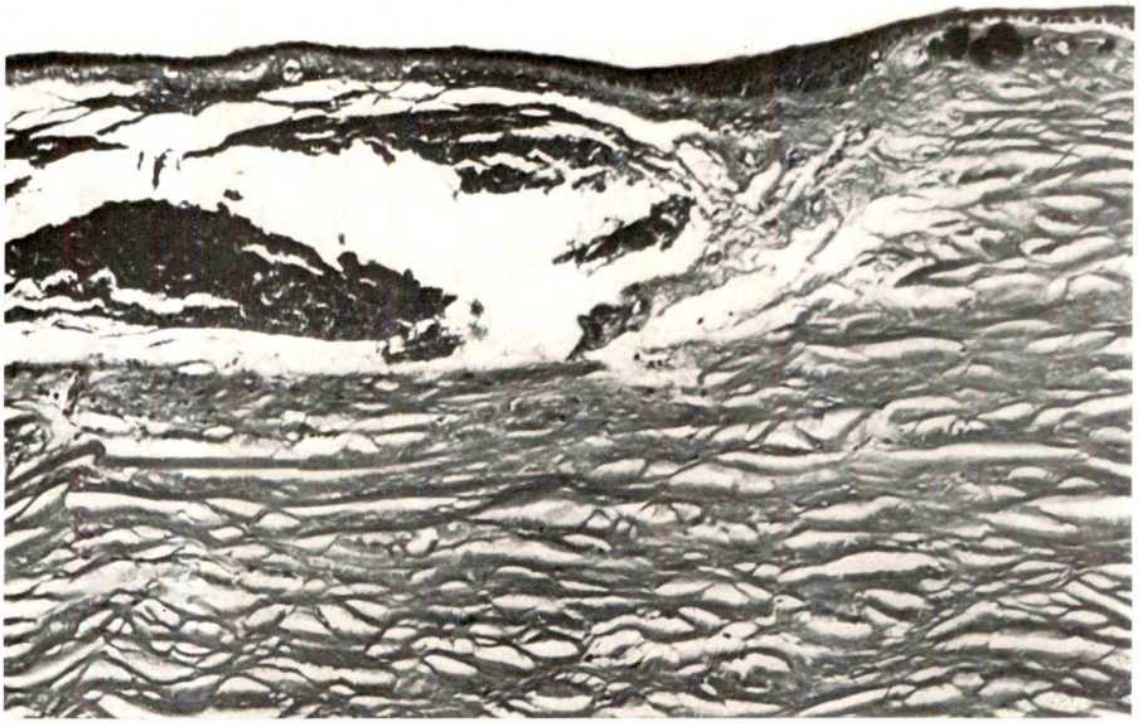
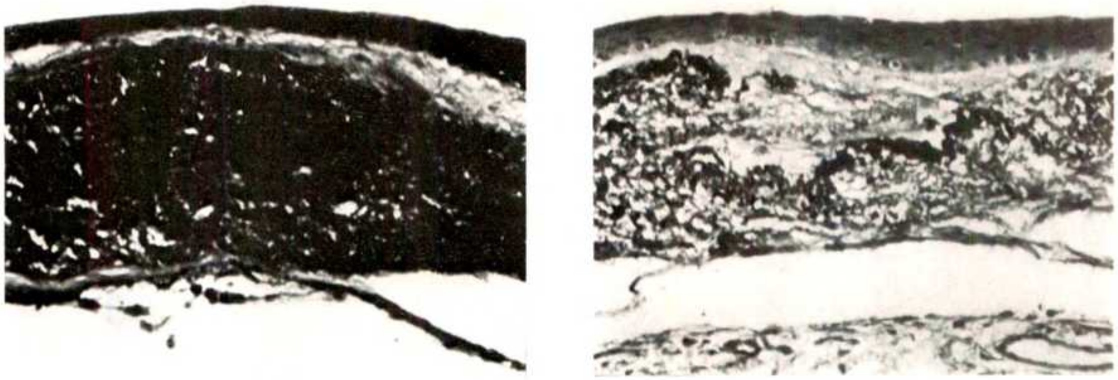


FIG. 3 *Section showing hyaline droplets immediately beneath epithelium of corneal periphery associated with coarse degenerate fibres of a bulbar conjunctival pinguecula. Verhoeff-van Gieson.* ×115



(4*a*) (4*b*)

FIG. 4 *Pinguecula.* (a) *Pseudoelastic fibres stain intensely with Verhoeff's haematoxylin.* (b) *Pretreatment with elastase for 6 hours partially inhibits staining reaction but coarse convoluted fibres continue to react. Verhoeff-van Gieson.* ×195

conjunctival droplets are the result of degenerative changes in the stromal collagen (Klintworth, 1972; Brownstein and others, 1973; Christensen, 1973; Rodrigues and others, 1975). This concept has much in its favour. Our finding, however, that despite a common propensity to stain by Verhoeff's procedure for elastic the ability of pingueculae to react with other elastic stains such as orcein and aldehyde-fuchsin is not shared by the spheroidal deposits, does suggest that the transition from degenerative collagen to spheroidal droplets is due to more than a simple process of fibrillar disintegration. Adequate explanation of these staining differences requires a better understanding of the elastotic change seen in pinguecula formation and more information concerning the chemistry of the

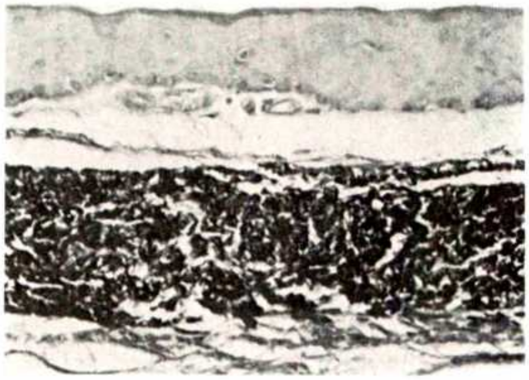
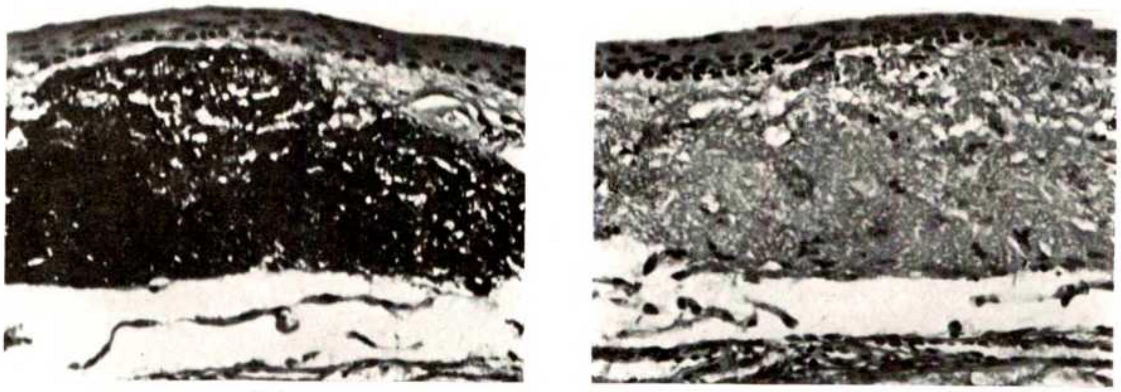


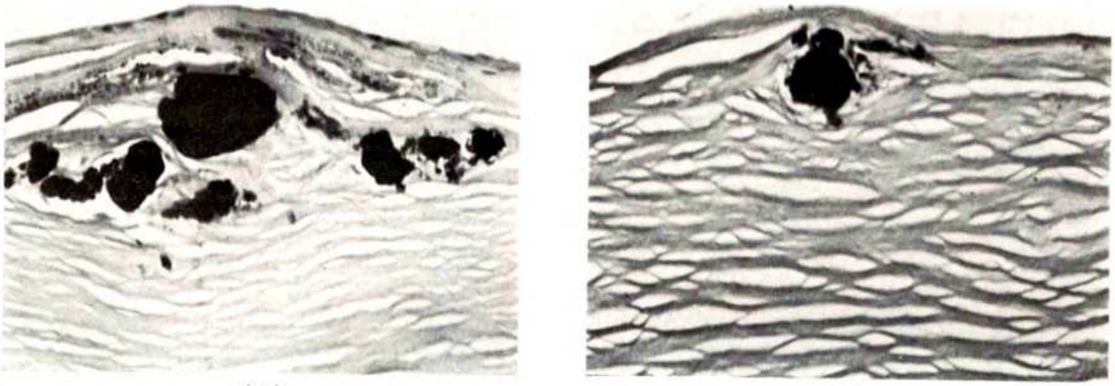
FIG. 5 *Pinguecula. Abnormal fibres stain blue with aldehyde-fuchsin and, apart from some less coarse fibres, are essentially unaffected by elastase. Gomori's aldehyde-fuchsin.* ×195

staining reactions, but they do point to a difference in composition between the deposits and elastotic collagen. The earlier finding of tryptophan and appreciable amounts of tyrosine and sulphur-containing amino-acids in the deposits (Garner, 1970; Klintworth, 1972; Brownstein and others, 1973; Garner, Morgan, and Tripathi, 1973) underlines this disparity, since these amino-acids are either absent or minimal in elastic tissue and collagen. The electron microscopy studies of Hanna and Fraunfelder (1972) may be relevant in this context, since they concluded that the spheroidal droplets represent the condensation of a granular material secreted by abnormal fibrocytes and deposited on collagen fibrils. Hogan and Alvarado (1967) have also commented on the presence of a non-collagenous protein in the spheroidal deposits. The addition of a second



(6*a*) (6*b*)

FIG. 6 *Pinguecula. Positive staining with orcein largely prevented by predigestion with elastase.* (a) *Without elastase;* (b) *with elastase. Orcein.* ×195



(7*a*) (7*b*)

FIG. 7 *Spheroidal droplets in cornea stain intensely with Verhoeff's haematoxylin and are unaffected by pretreatment with elastase.* (*a*) *Before elastase;* (b) *after elastase. Verhoeff-van Gieson.* ×195

protein, from whatever source, to the altered collagen fibres of a pinguecula (or to altered corneal stroma) might account for the somewhat different staining properties.

With regard to the staining properties of the pingueculae themselves, it is to be noted that we observed variable but generally marginal loss of ability to react with Verhoeff's haematoxylin and aldehyde-fuchsin as a result of predigestion with elastase and complete inhibition of orcein staining in such preparations. This effect of elastase is at slight variance with the usual statement that the fibres of a pinguecula are resistant to this type of enzymatic activity (Cogan, Kuwabara, and Howard, 1959) and is not easily explained, although it is of interest that Lever (1967) states that elastotic fibres in the skin are digested.

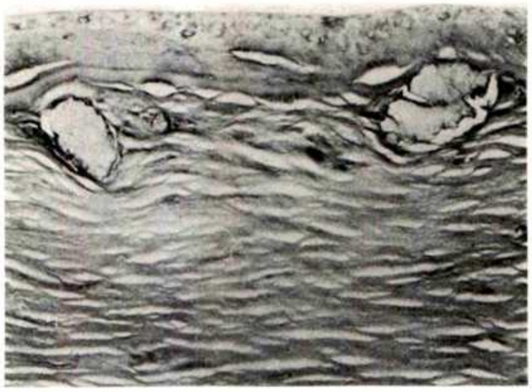


FIG. 8 *In contrast to fibres of pingueculae, spheroidal droplets do not react with Gomori's aldehyde-fuchsin.* ×130

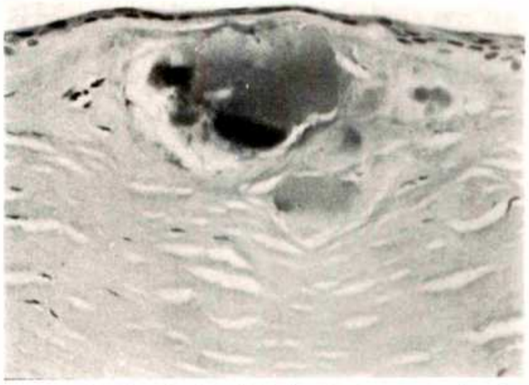


FIG. 9 *Section of spheroidal droplets in cornea showing absence of staining with orcein.* ×195

NOMENCLATURE

Increased interest on the part of a number of investigators coupled with a persistent lack of crucial data has led to a profusion of names for the hyaline deposits. The term keratinoid, introduced by Garner (1970, 1972), has not found general acceptance and, in the light of subsequent evidence linking the deposits with elastotic degeneration of collagen, is probably best abandoned. Some recent terms such as proteinaceous degeneration (Christensen, 1973) are too vague, whereas others, such as actinic (Klintworth, 1972) or climatic (Freedman, 1973a) keratopathy, are not only

Table I *Staining reactions for elastic tissue in patients with pingueculae and/or corneal droplets*

Case no.	*Pingueculae*						*Spheroidal droplets*			
	Before elastase			*After elastase*			*Verhoeff*		*Aldehyde-fuchsin*	*Orcein*
	Verhoeff	*Aldehyde-fuchsin*	*Orcein*	*Verhoeff*	*Aldehyde-fuchsin*	*Orcein*	*Before elastase*	*After elastase*		
1		+	+			−				
2		+	+			−				
3		+								
4	+		+	±		−				
5	+	+	+	+	+	−				
6	+	+	+	+	+	−				
7	+	+	+	+	+	−	+		−	−
8	+		+	±		±	+	+		−
9	+		+			−	+			−
10							+	+	−	−
11							+	+	−	−
12							+	+	−	−
13							±	±	−	−
14							+	+	−	−

unproved but are also unduly restrictive since they do not account for the corneal deposits secondary to other corneal disease. Until the nature of the deposits is known and their aetiology substantiated it may be better to use a purely descriptive term such as spheroidal degeneration or droplet keratopathy.

Summary

A study of almost 1000 outpatients at a London eye hospital showed the presence of asymptomatic yellowish, spheroidal deposits in the peripheral cornea or conjunctiva, or both, in about 6 per cent, with a preponderance of males and older subjects among those affected. This prevalence is less than is observed in people in countries exposed to higher levels of sunlight.

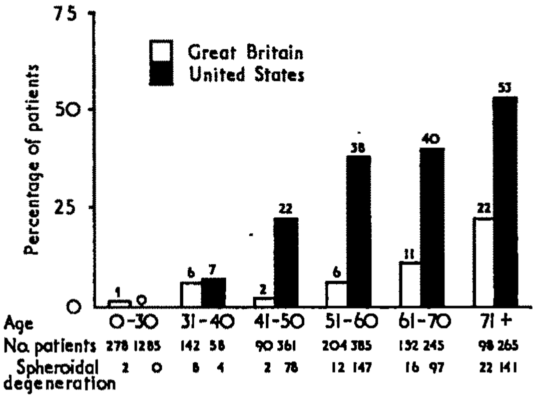


FIG. 10 *Comparison of prevalence of spheroidal droplets in conjunctiva and/or cornea in Great Britain and United States of America at various ages*

Table II *Reported prevalence of spheroidal droplets in various parts of the world (not age- or sex-matched)*

Geographical location	*Prevalence of spheroidal droplets in general population (percentage)*	*Reference*
Dahlak Island, Ethiopia	57	Rodger, 1973
Nama, South-West Africa	31	Freedman, J., 1973b
Arkansas, USA	18	Fraunfelder and Hanna, 1973
Labrador, Canada	11	Freedman, A., 1965
Labrador, Canada	14	Young and Finlay, 1975
London, England	6	Present study

Histological study of the deposits showed some tinctorial similarities with the pseudoelastic fibres of pingueculae, with which they were sometimes associated, but also significant differences suggesting that the spheroidal deposits might be a composite of degenerate collagen and a second non-collagenous protein.

Until a more precise terminology is feasible we suggest that a purely descriptive name such as spheroidal degeneration or droplet keratopathy should be used to describe this entity.

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Contact lenses at high altitude: experience on Everest south-west face 1975

CHARLES CLARKE
The Middlesex Hospital, London

Although contact lenses have been worn for several decades by Alpine climbers, skiers, and civilian aircraft personnel there is no record of their use on expeditions to altitudes higher than 15 000 ft (4560 m), and in particular to Himalayan peaks where supplementary oxygen is required. Thus a record of the experience of those members of the British Everest Expedition who wore or tried to wear contact lenses at high altitude during the autumn of 1975 is of interest.

Subjects and results

Five members were fitted with Permalenses during the spring and early summer and, after some initial problems with fitting, all became accustomed to wearing them continuously in Britain. One man climbed to 20 000 ft (6080 m) in the Karakoram before the Everest expedition and was able to use the lenses, and a second, a mountaineering camera man, had no difficulties with them during work in Europe.

The 1975 Everest expedition may conveniently be divided into three stages. (1) The march across Nepal to base camp at 18 000 ft (5472 m) in the monsoon weather of August. (2) The climb from base to camp 4 on the south-west face at 24 000 ft (7296 m). This was done without supplementary oxygen. (3) Work above 24 000 ft, when oxygen was usually used while ascending and at a reduced rate while sleeping.

During the three-week approach to base camp there was little reason to expect problems. The group were travelling in warm, moist weather with temperatures up to 35°C. This period served as a useful time to assess the motivation of the five climbers to continue to use the lenses on the mountain. Three had had great problems on previous trips with glasses misting up, and were thus keen to use them higher. One, on his own admission, was careless and found that he was unable to refrain from rubbing his eyes in the mornings: he lost the original pair of lenses and soon lost another pair. The other climber had had little trouble with glasses and found he simply preferred them.

The second part of the expedition up to 24 000 ft was wholly on snow and ice, and by day everyone wore either goggles, a screen, or sunglasses with side pieces. Quite apart from the need to avoid snow blindness, the eyes were thus shielded from wind and spindrift. One of the three remaining lens users thought that his visual acuity was poorer than with glasses and, although vision on testing was 6/6 bilaterally, he preferred to remove the contact lenses. The other two lens users changed to spare lenses on two occasions during this three-week period after the lenses had slipped from the cornea during the night. Otherwise they found the lenses very acceptable. These two climbers worked on the mountain above 24 000 ft. The Blume-Robertshaw demand oxygen system was used by day with a close fitting mask which covered only the mouth and nose, while at night a looser polythene mask was used on a constant flow system. Both climbers finally stopped using the lenses at about 26 000 ft (7904 m), each after several days. On one occasion a lens slipped in the night and there was moderate conjunctivitis. Of the remaining climber, our camera man, it is known that his lenses were uncomfortable and that he had reverted to glasses by the time of his death near the summit of Everest. These results are summarized in the Table.

Table *Duration of continuous wear of hydrogel contact lenses at high altitude*

Subject	*Periods of continuous wear (days)*	*Comments*
A	4 (5000 to 8000 ft)	Initial pair lost after two days. Poorly motivated
B	3 (5000 to 8000 ft)	Preferred glasses
C	12 (5000 to 19 000 ft)	Preferred glasses
D	(a) 40 (sea level to 18 000 ft)*	Lost lens in a bivouac
	(b) 14 (5000 to 18 000 ft)*	Lens slipped at night
	(c) 10 (20 000 to 26 000 ft)*	Lenses uncomfortable Two changes of lenses during (c)
E	Over 50 (5000 to 26 000 ft)	Two changes when a lens slipped during night but no rest periods without lenses

*Rest periods of about 2 weeks each divided these continuous periods

1000 feet = 304 metres

Discussion

Although contact lens practitioners have commented on the difficulties which wearers have in cities as low as Denver, Colorado (Harper, 1973), it is striking that two men on this expedition were able to use hydrogel lenses up to 24 000 ft. The eyes of all members of the team were examined often (as part of a study of high altitude retinal haemorrhages and to measure the intraocular pressure) and it was not clinically noticeable that the two long-standing contact lens wearers had more conjunctival injection than their colleagues. In both cases a limited examination of the cornea was normal. Illumination was provided by a slit light of a 12-volt Keeler Pantoscope and the 13D achromatic condensing lens was used as an objective. The cornea was then stained with fluorescein.

The ambient oxygen tension at 20 000 ft is of the order of 65 mmHg and at 24 000 ft 55 mmHg. At the summit of Everest it falls to about 45 mmHg. The minimum surface oxygen tension for normal corneal function is said to be of the order of 15 mmHg (Fatt, 1971 and 1972; Polse and Mandell, 1970) and it is interesting to speculate how nearly this critical level is reached at high altitude, particularly during sleep. We were surprised to find the lenses well tolerated by two climbers below 24 000 ft and doubtless they will be used again by high altitude mountaineers.

Summary

Five members of the British Everest Expedition 1975 were equipped with hydrogel contact lenses. Some clinical observations are made about the performance of these lenses. Two men were able to use them up to an altitude of 24 000 ft, where the ambient oxygen tension is of the order of 55 mmHg.

I thank Mr John Evans, of Global Vision (UK) Ltd, and Mr John de Carle for their help in supplying and fitting the lenses, and Professor Irving Fatt, of the University of California, Berkeley, Wing Commander Brennan, and Squadron Leader Denison of the Royal Aircraft Establishment for guidance. The ocular studies on Everest were financed by a grant from the Department of Neurological Studies, the Middlesex Hospital.

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Acute endocrine exophthalmos

PETER T. C. DOCHERTY
From the North Staffordshire Royal Infirmary, Stoke-on-Trent

The onset of endocrine exophthalmos is generally slow and any variations are gradual. However, it can develop suddenly (within minutes—Dock, 1915; overnight—Falta, 1913). When assessing the progress of exophthalmos, it is important to use an exophthalmometer, as the degree of chemosis and the variations in the width of the palpebral fissure can be deceptive. Many reports of dramatic changes in the degree of exophthalmos lack the support of exophthalmometric readings.

It has been noted (Werner, 1966; Pinchera, Pinchera, and Stanbury, 1965; Liddle, Heysell, McKenzie, 1965; Eversman, Skillern, and Senhauser, 1966; Fox and Schwartz, 1967) that endocrine exophthalmos may occur in the euthyroid state and in patients who have never had thyrotoxicosis.

Case report

A 60-year-old man presented at the ophthalmic unit as an emergency on 11 March 1975. He had a 24-hour history of pain, redness, watering, swelling, and some deterioration of visual acuity in the right eye. He also complained of double vision. There was no history of trauma.

Ocular examination revealed a moderate degree of right axial proptosis. The visual acuity was 6/9. The conjunctiva was chemotic. No pulsation of the globe could be detected and the proptosis was virtually irreducible. There was no cranial bruit. Ocular movements of the right eye were grossly limited in all directions with almost complete absence of elevation. The cornea was intact and lid closure was full. Visual acuity in the left eye was 6/6 and this eye appeared to be normal. Exophthalmometer readings were 22 mm right eye, 17 mm left. Visual field examination showed no field defect (Goldmann perimeter). Skull *x* ray revealed a soft-tissue mass in the right orbit. The carotid pulses and fundi were normal.

General examination showed the patient to be rather sluggish, both mentally and physically, and he did not give a clear history of his illnesses. He did not seem to be unduly concerned about his eye condition. He had no fever and the pulse rate and blood pressure were normal.

A routine urine analysis showed a level of 2 per cent sugar and a random blood sugar was found to be 258 mg/100 ml. The patient then stated that he was a diabetic but 'had got over all that now'. His medical records showed that he had been a known diabetic for 4 years, controlled on 1000 calorie diet and one tablet of phenformin 50 mg daily. He had been a persistent defaulter from the diabetic clinic.

The patient was admitted to the eye unit. In view of the findings, the possibility of a localized orbital cellulitis was considered, and treatment was started with local and systemic antibiotics.

12 MARCH 1975

The proptosis in the right eye had increased, and, during the night, the left eye had also become proptosed, to an even greater extent than the right (Figs 1*a*, *b*, *c*). There was now chemosis on both sides and a marked restriction of ocular movements. The corneae remained intact, but lid closure was becoming difficult. Exophthalmometer readings were 24 mm right eye, 25 mm left. The intraocular pressure by applanation tonometry was 40 mmHg right eye, 28 mmHg left. Acetazolamide tablets 250 mg four times daily were added to the treatment. Because of the clinical picture now presenting, a diagnosis of acute endocrine exophthalmos was made.

13 MARCH 1975

The chemosis was more marked and the patient had great difficulty in closing his eyes. The corneae were intact (Figs 2*a*, *b*, *c*).

Treatment was started with systemic steroids, prednisolone 60 mg daily. Exophthalmometer readings were 24 mm right eye, 25 mm left. The visual acuity was 6/9 right eye, 6/12 left. Intraocular pressures were 36 mmHg right eye, 48 mmHg left.

14 MARCH 1975

The exophthalmos had further increased. The degree of chemosis was unchanged and the patient was still able to close both eyes, but with extreme difficulty. Both corneae remained intact. Drops of adrenaline 1 per cent twice daily were instilled into each eye. The right visual field showed slight constriction and a fundus examination revealed early papilloedema on both sides.

Exophthalmometer readings were 26 mm right eye, 27 mm left. The visual acuity was 6/9 right eye, 6/12

Address for reprints: P. T. C. Docherty, FRCS, Senior Registrar, Ophthalmic Unit, North Staffordshire Royal Infirmary, Stoke-on-Trent, Staffordshire

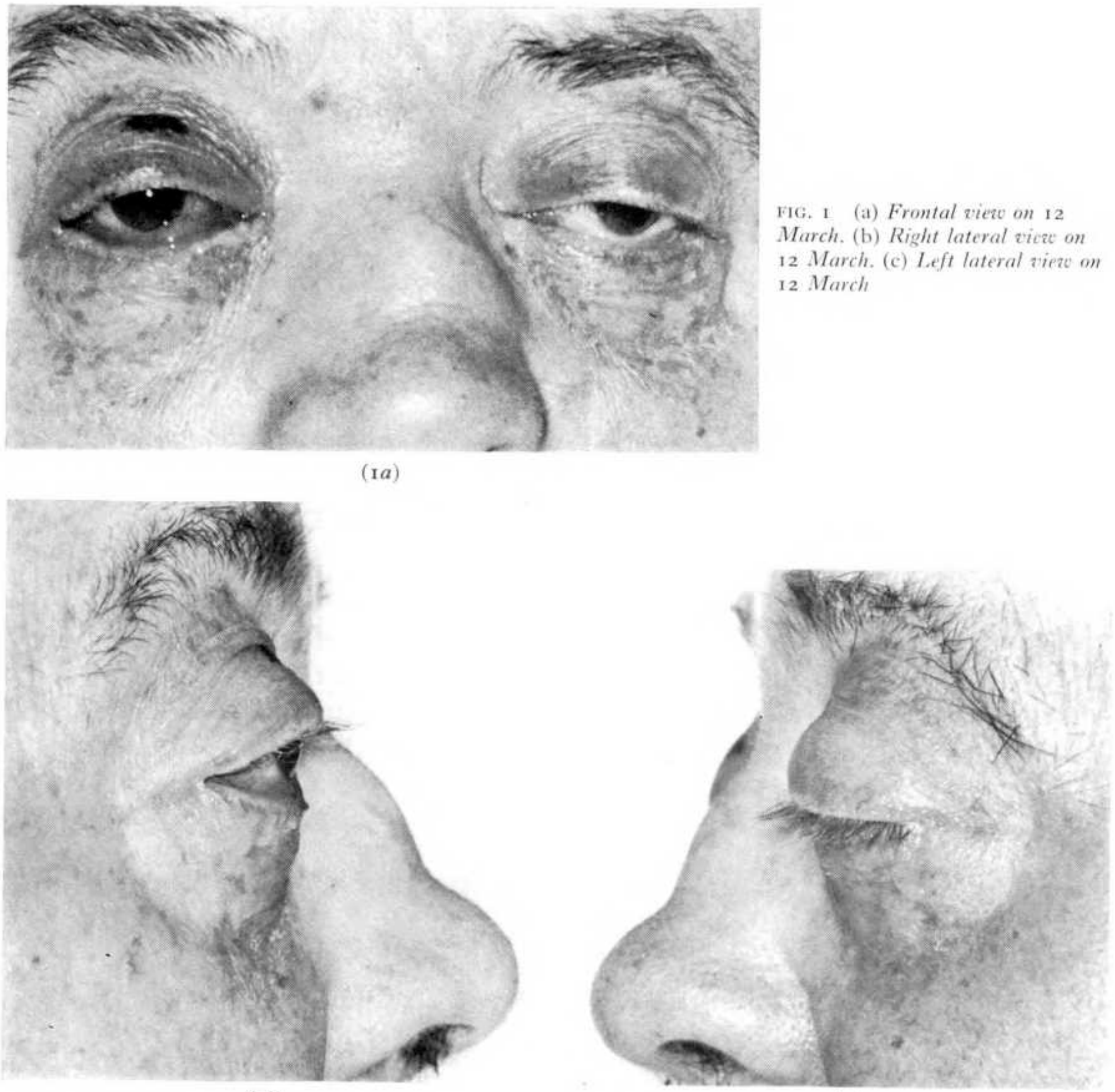

FIG. 1 (a) *Frontal view on 12 March.* (b) *Right lateral view on 12 March.* (c) *Left lateral view on 12 March*

(1*a*)

(1*b*)

(1*c*)

left. Intraocular pressures were 23 mmHg right eye, 32 mmHg left.

In view of the deterioration, it was felt that a decompression procedure might be necessary, and a consultation was arranged with a neurosurgeon for the next day. The dosage of prednisolone was increased to 120 mg daily (Kinsell, Partridge, and Foreman, 1953; Werner, 1966; Wright, 1970).

15 MARCH 1975

A marked improvement was noted. The chemosis was much less, the ocular movements were less restricted, and the visual fields had returned to normal. The papilloedema noted on the previous day had disappeared.

Treatment was continued with 120 mg prednisolone daily.

Exophthalmometer readings were 21 mm right eye, 24 mm left. The visual acuity was 6/9 right eye, 6/9 left. Intraocular pressures were 22 mmHg right eye, 22 mmHg left.

16 MARCH 1975

Improvement continued. The chemosis had nearly disappeared and the ocular movements were almost normal with a slight restriction of elevation.

Exophthalmometer readings were 21 mm right eye, 24 mm left. The visual acuity was 6/6 partial right eye, 6/6 partial left. Intraocular pressures were 20 mmHg right eye, 21 mmHg left.

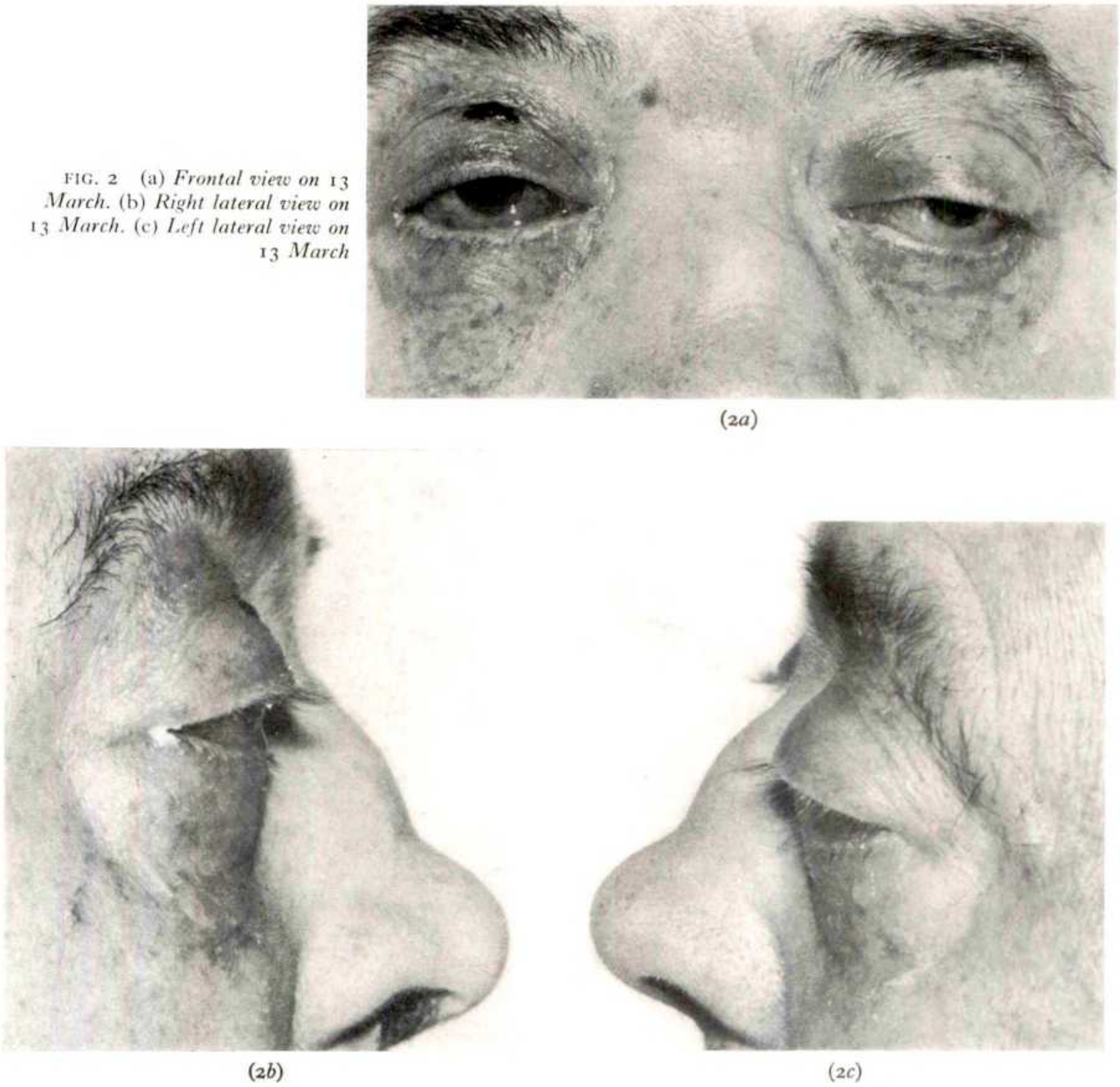

FIG. 2 (a) *Frontal view on 13 March.* (b) *Right lateral view on 13 March.* (c) *Left lateral view on 13 March*

(2*a*)

(2*b*)

(2*c*)

17 MARCH 1975

Exophthalmometer readings were 20 mm right eye, 23 mm left. The visual acuity was 6/6 partial right eye, 6/6 partial left. Intraocular pressures were 17 mmHg right eye, 20 mmHg left. The dosage of prednisolone was reduced to 60 mg daily.

19 MARCH 1975

Exophthalmometer readings were 18 mm right eye, 23 mm left. The dosage of prednisolone was reduced to 30 mg daily.

21 MARCH 1975

Exophthalmometer readings were 18 mm right eye, 22 mm left.

24 MARCH 1975

Exophthalmometer readings were 18 mm right eye, 21 mm left.

25 MARCH 1975

The patient was discharged. He was prescribed prednisolone 20 mg daily, chlorpropamide 250 mg daily, and phenformin SR 50 mg twice daily. He was restricted to a 1000 calorie diet.

4 APRIL 1975

Exophthalmometer readings were 16 mm right eye, 17 mm left. The dosage of prednisolone was reduced to 15 mg daily.

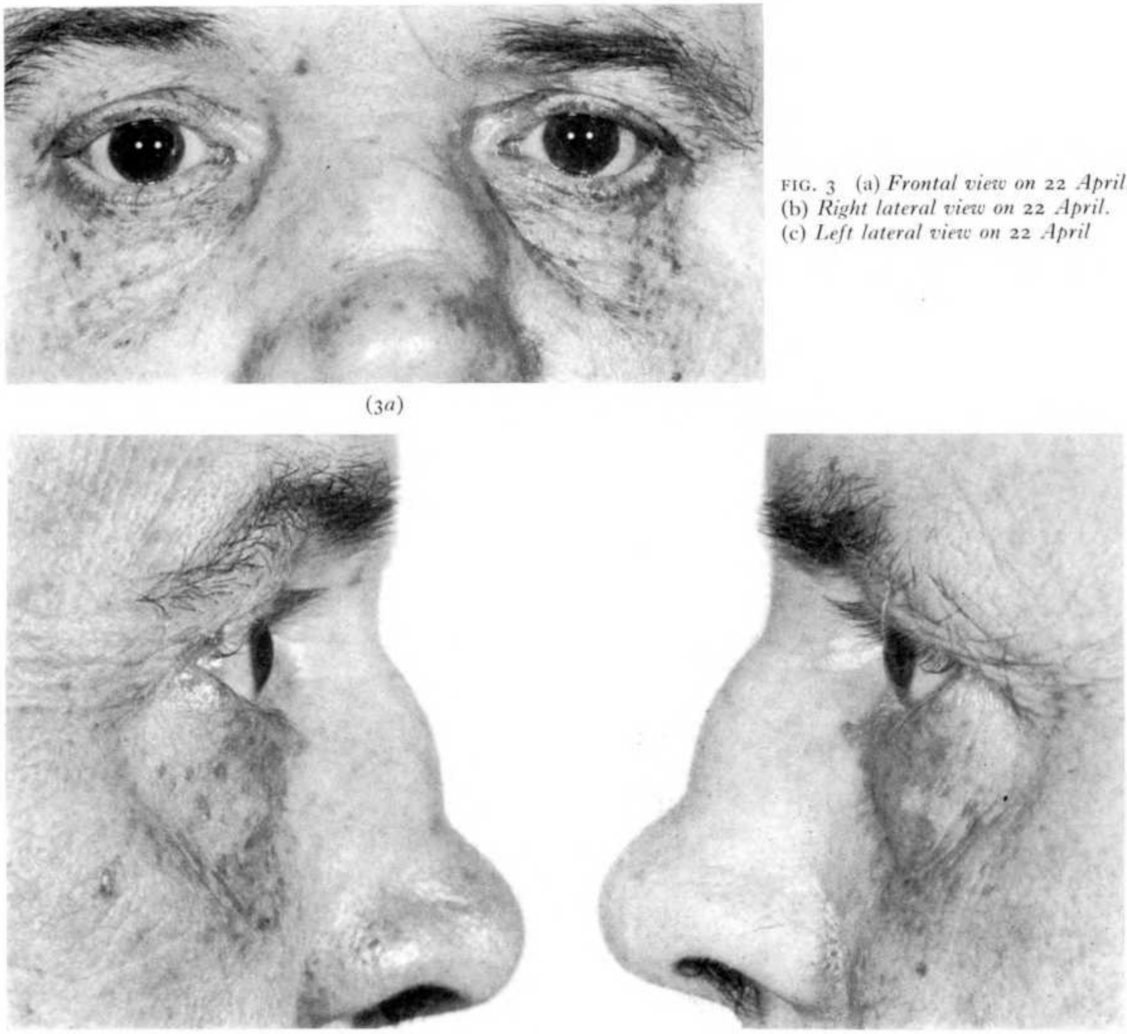

FIG. 3 (a) *Frontal view on 22 April.* (b) *Right lateral view on 22 April.* (c) *Left lateral view on 22 April*

(3*a*)

(3*b*)

(3c)

22 APRIL 1975

The patient was reviewed at the ophthalmic unit. The chemosis had completely disappeared and the ocular movements were full (Figs 3*a*, *b*, *c*). Exophthalmometer readings were 15 mm right eye, 16 mm left. The visual acuity was 6/6 partial right eye, 6/6 left. The intraocular pressures were 16 mmHg right eye, 17 mmHg left. The dosage of prednisolone was reduced to 5 mg daily.

30 MAY 1975

Prednisolone was discontinued and the eyes remained normal. Exophthalmometer readings were 15 mm right eye, 16 mm left. The response is summarized in Fig. 4.

INVESTIGATIONS

Haemoglobin	16·7 g/100 ml
White blood count	10 600/cm
Blood urea	40 mg/100 ml
Sodium	131 mmol/l
Chloride	92 mmol/l
Potassium	3·6 mmol/l
Creatinine	0·7 mg/100 ml
CO$_2$	21 mmol/l
Blood glucose	258 mg/100 ml
Bilirubin	1·5 mg/100 ml
Cholesterol	438 mg/100 ml
Plasma calcium	11·1 mg/100 ml
Uric acid	4·4 mg/100 ml
Alkaline phosphatase	87 mU/ml
Albumin	4·6 g/100 ml
Inorganic phosphate	4·1 mg/100 ml
Total protein	7·8 g/100 ml

The Wassermann reaction and Kahn test were negative. *X* rays of the right orbit, sinuses, and skull, were taken on 11 March and showed an opacity of soft tissue density in the lower part of the right maxillary antrum

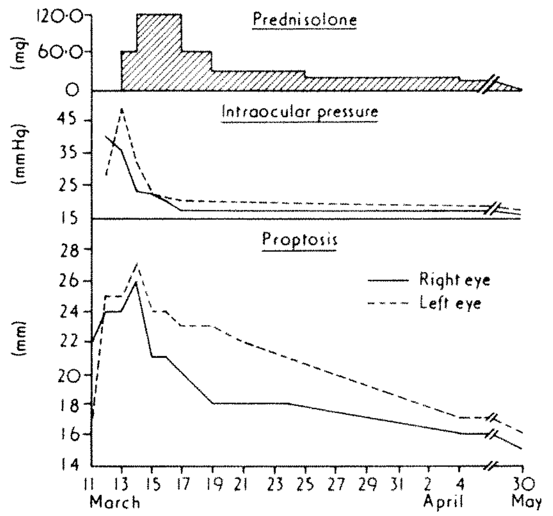

FIG. 4 *Graph showing ocular response to systemic steroids*

with a smooth upper border. No associated bone destruction was identified and it seems likely that this was a polyp. There was a considerable difference in the density of the orbits, that on the right showing an overall opacity consistent with the soft tissue swelling. No definite bone destruction was seen. Thyroid function tests showed a thyopac 3 value of 118·8, and thyopac 4 of 11·8 μg per cent, with a free thyopac index of 9·9 which is normal.

A thyrotrophin releasing hormone (TRH) test showed an impaired response which suggested partial thyroid autonomy. At 0 min thyroid stimulating hormone (TSH) was 1·6 mU/l, at 20 min 3·9 mU/l, and at 60 min 3·0 mU/l. Thyroid antibodies were all negative.

Discussion

The unusual features of this case were the rapidity of onset—the proptosis in the right eye developing probably within 24 hours, and that in the left within six hours—and the rapidity and completeness of the response to systemic steroids (Brown, Coburn, Wigod, Hiss, and Dowling, 1963).

In other cases reported (Hoffenberg and Jackson, 1958; Brown and others, 1963; Werner, 1966) there was also rapid response to steroid therapy, but in only one case did the condition clear rapidly. Whether coincidentally or not, the patient was, like the case reported here, a clinically euthyroid diabetic. Further study into the possible connexion between acute endocrine exophthalmos and diabetes could prove fruitful.

Ideally, this condition should be treated by the ophthalmologist in collaboration with the physician; the former observing the state of the corneae, fundi, ocular fields, and the degree of exophthalmos, and the latter observing the patient's physical and biochemical response to the large doses of steroids.

It has been stated (Duke-Elder, 1974) that in the treatment of endocrine exophthalmos, large doses of systemic steroids usually need to be administered over a considerable period of time, with the inevitable hazard, not only of systemic complications, but also of the ocular side-effects such as cataracts and elevation of the intraocular pressure (Haddad, 1968).

Fortunately, in this case, the response was so rapid that it was possible to reduce the dosage before any such hazards were encountered.

Three months after complete cessation of drug therapy, there was no evidence of any recurrence of the condition. Whether this resolution will be permanent remains to be seen.

Summary

A case is reported of acute endocrine exophthalmos in a 60-year-old clinically euthyroid male diabetic and the rapid response to steroid therapy is described. The exophthalmometer was used to assess objectively the variations of the exophthalmos.

I am indebted to Mr P. J. M. Kent and Dr W. Van't Hoff for permission to quote their case, and Mr W. G. Coddington for his constructive advice, and to the Department of Medical Illustration for the photographs.

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Cadaver bone as orbital implant

R. K. BANSAL
From the Department of Ophthalmology, University of Nigeria Teaching Hospital, Enugu, Nigeria

Orbital implants are used to provide a mobile ball for a prosthesis to pivot on and also to prevent bony deformity of the orbital wall. Various types have been tried. Acrylic, now most commonly used, is a comparatively biologically inert substance and if proper care is taken to maintain asepsis, to achieve correct anatomical placement, and to bury the implant in a reasonably thick layer of tissue the chances of extrusion are less. But late pressure necrosis of the tissue over the implant by the artificial eye is not uncommon. Therefore individually moulded prostheses are usually required (Reed, 1964).

Synthetic polyvinyl sponge (Pearlman, 1958) does not migrate easily, as it gets organized with the host tissue, but it is more susceptible to infection. Moreover, its removal is tedious and difficult. Spaeth (1941) recommended the use of Guist's carbonized cancellous bone spheres for orbital implants, and Molteno, Van Rensberg, Van Rooyen, and Ancker (1973) have used kiel bone, an antigen-free cancellous calf bone, with good results. All other materials like glass, fat, rubber, wire, silk, fascia lata, donor sclera, and others have been condemned and are no longer used.

This paper reports a trial of cadaver bone as a buried orbital implant.

Patients and methods

The patients were selected from those coming to the outpatient department with an indication for enucleation. Fifty-four patients whose ages ranged from 8 to 54 years were operated on. The indications for enucleation were as follows: blunt injury to eye 28 cases, recent perforating injury seven cases, absolute glaucoma 15 cases, and atrophic bulbi four cases. Any infection was medically treated before operation.

Cadaver flat ribs were obtained from the university department of anatomy. The bone was thoroughly cleaned. Various sizes of implants were cut with a bone cutter. The grooves were made by saw on four sides to accommodate the recti (Fig. 1). The implants were sterilized before use by autoclaving.

OPERATIVE TECHNIQUE

Under general anaesthesia the eye ball was exposed with the help of an eye speculum. The conjunctiva and Tenon's capsule were cut along the limbus and retracted. Each rectus was caught on a strabismus hook and a 3/0 chromic catgut suture applied near the insertion. The muscle was then detached near the insertion and clipped on to the towel with artery forceps. The inferior oblique and superior oblique were sutured to the lower margin of the lateral rectus and superior rectus respectively by 3/0 chromic catgut to prevent the migration of the implant towards the floor of the orbit. The optic nerve was crushed by artery forceps and cut. The eyeball was prolapsed out and all its attachments cut.

The four recti were pulled out and a bed for the implant prepared by achieving as much haemostasis as possible by hot sponging. An implant of the correct size was selected and placed in the floor of orbit. The four recti were placed in their respective grooves (Fig. 2). They were pulled tight and the opposite recti sutured over the implant with 3/0 chromic catgut. The four recti were then united by another 3/0 chromic catgut suture (Fig. 3). Tenon's capsule was sutured vertically by 4/0 chromic catgut with interrupted sutures. The conjunctiva was stitched by continuous 6/0 black silk suture. Soframycin eye ointment was inserted and a pad and crepe bandage applied.

The first dressing was done after 48 hours and was followed by routine daily dressings of soframycin eye ointment. Systemic antibiotics were used only when necessary. The conjunctival suture was removed after six days. Artificial eyes were fitted as soon as possible, usually after three to four weeks.

Results

Out of 54 cases with a follow-up of six months to three years only two implants were extruded. One was extruded within five days of operation. This was because the patient had a lacerated eyeball and possibly some infection. The other extrusion, after one year, was in a young girl who had a very tight artificial eye which she wore even during the night.

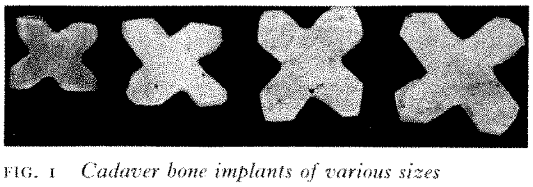

FIG. 1 *Cadaver bone implants of various sizes*

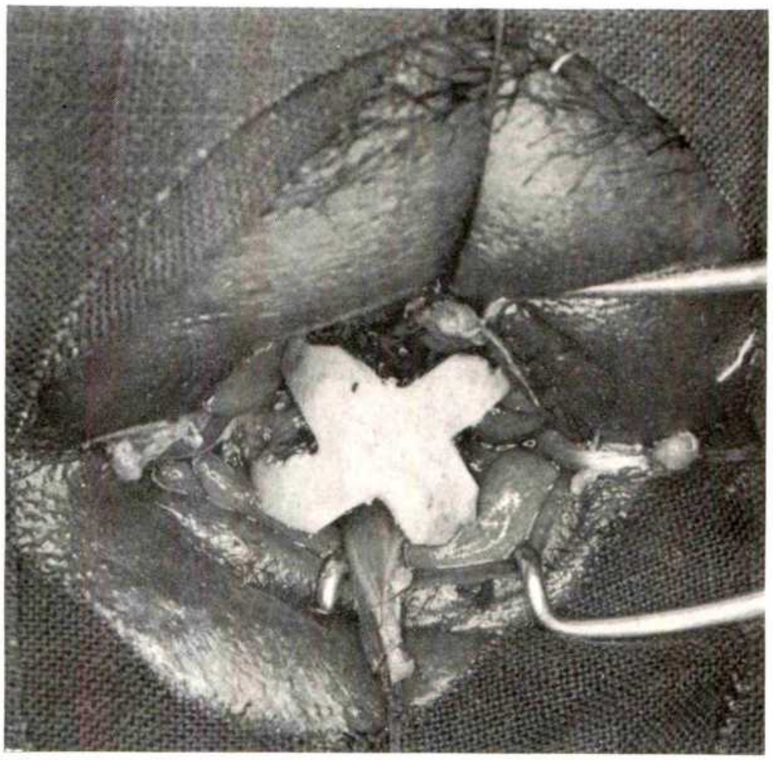

FIG. 2 *Implant placed in floor of orbit after stretching of recti*

The resulting ulceration of the conjunctiva and infection was not controlled in time. In all other cases there was some initial postoperative oedema which subsided in three to four days. In long-term follow-up the conjunctiva was seen to be adherent and uniformly thinned out. Radiologically no change was seen in the radiodensity of the implant after three years (Fig. 4). The implants moved fully and freely.

Discussion

The results of bone implant, compared with acrylic or polyvinyl sponge implants, have been very encouraging. Moreover, cadaver bone is easily

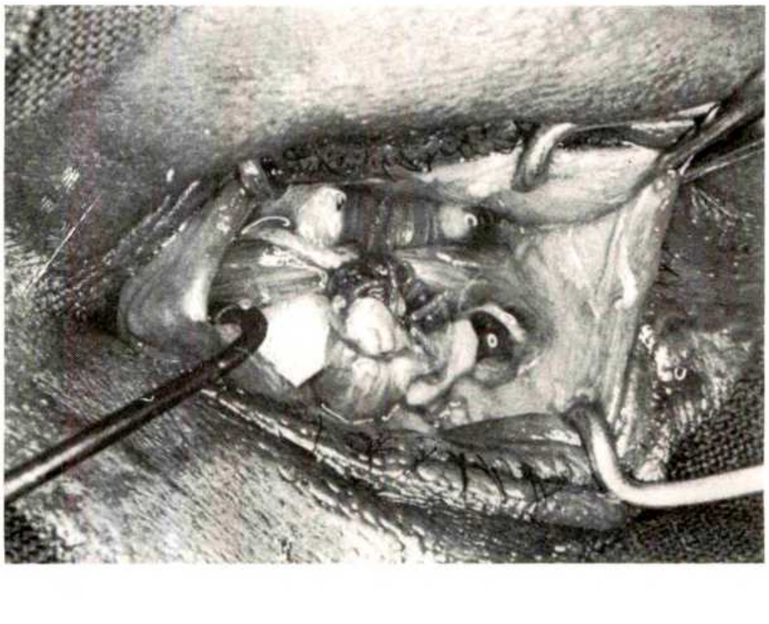

FIG. 3 *Four recti sutured over implant*

available and costs the patient nothing. Different sizes of implant can be prepared in advance and the appropriate one chosen at operation. There was no case of exposure of the implant, as reported by Molteno and others (1973), probably because Tenon's capsule and conjunctiva were sutured in two different layers at right-angles to each other. Similarly, in no case did the implant seem to migrate towards the floor. The purpose of suturing the inferior oblique muscle to the lower margin of the lateral rectus and the superior oblique to the superior rectus was to prevent this (Stallard, 1965).

A longer follow-up is needed to know the ultimate fate of the implants, but to date there is no radiological evidence of atrophy or shrinkage. Muscles should get a better anchorage on a bone implant because of its rough surface compared with an acrylic or silicone implant.

Summary

Fifty-four cases of cadaver bone orbital implant are described. The results were encouraging. Cadaver bone implant is easily available and can be prepared in various sizes to fit the individual patient.

I thank Mrs P. Gupta, of the Department of Anatomy, for helping me to prepare the bone implants and Mr A. J. Brooks, Head of Department of Medical Illustration, for the photographs.

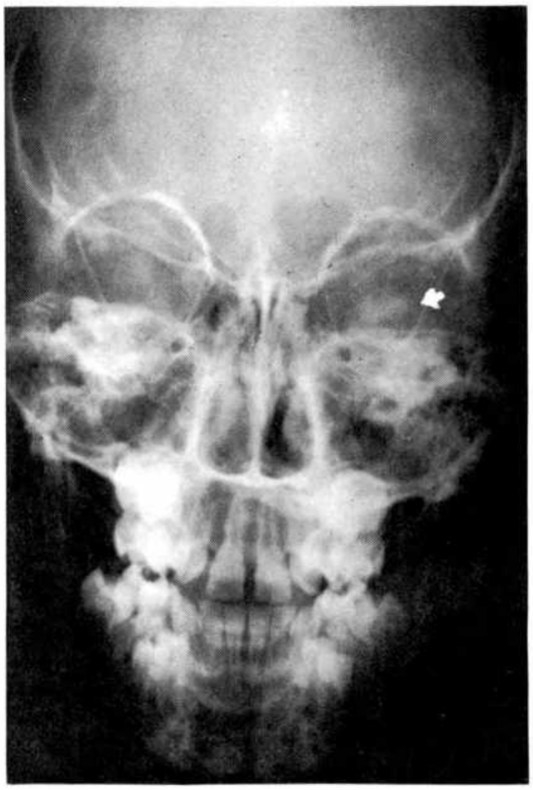

FIG. 4 *Radiological appearance of implant after 3 years*

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Book reviews

Reconstructive and Plastic Surgery of the Eyelids. By F. P. ENGLISH and W. A. KEATS. 1975. Pp. 95, figs. Thomas, Springfield, Ill. ($11)

This book begins with a chapter on basic techniques but it also includes less accepted procedures such as the transfer of full-thickness composite eyelid grafts from one eyelid to another. It continues with a series of short chapters describing a wide range of different surgical procedures which the authors use in the orbital region. These are extremely well and copiously illustrated with excellent diagrams as well as clinical photographs. The book is commendably brief and only the salient features of the different techniques are described. It is orientated towards presenting the authors' techniques to the practising ophthalmic surgeon and not to reviewing established procedures. The clinical indications for any particular procedure are not discussed in any detail relative to the available alternatives, and therefore this is not a good book for the embryo ophthalmologist who wants to see the whole subject in perspective. There must, however, be limitations with any book of this size and what Mr English and Mr Keats do achieve is a dynamic presentation of ideas which should provide the practising ophthalmologist with some useful additional techniques when operating in the eyelid region. J. R. O. COLLIN

Symposium of Glaucoma: Transactions of the New Orleans Academy of Ophthalmology. By D. R. ANDERSON, S. M. DRANCE, M. A. GALIN, J. R. LYNN, S. M. PODOS, K. T. RICHARDSON JR, and R. N. SHAFFER. 1975. Pp. 387, figs, tables, refs. Mosby, St Louis; Kimpton, London (£17·80)

This book contains the papers presented and the round table discussions at the twenty-third session of the New Orleans Academy of Ophthalmology in 1974. The subject was glaucoma, and the contributors' photographs at the beginning of the book reveal expressions of faint surprise, subdued scepticism, and friendly cheerfulness, all of which were doubtless displayed from time to time throughout the symposium. Judging from the papers and discussions, one feels bound to conclude that the meeting must also have evoked sustained interest, because many aspects of glaucoma received attention and the contributors always had something to say which was based on their own special knowledge or experience.

Topics are not arranged in any particular order but nothing seems to have been lost by the abandonment of the usual arrangement. The various sections on surgical procedures contain detailed descriptions with many practical tips based on wide experience, and are generally well illustrated by simple drawings. The style ranges from the formal to the chatty, a variation which keeps reminding us that we are reading the reports of a meeting and which recreates for us, perhaps, the atmosphere that prevailed.

There are two sections by Richardson on drug delivery systems. The usual way of giving a drug is by doses, and this applies to substances administered orally and to those instilled as drops into the eye. This means that the concentration of the drug in the tissues is initially high, becoming lower as the time after the first dose increases and the time for the next dose approaches; therefore there tends to be an overdosage—underdosage sequence with its attendant disadvantages. The system to be preferred is one which releases a drug where it is required at a constant rate. The various possibilities are discussed not only in general, but also as they apply to the eye. A few such systems are already in use and their future development certainly warrants close study.

In another section, Anderson looks critically at the various hypotheses of glaucomatous cupping and finds them lacking in some respects. He suggests that raised intraocular pressure causes glial damage in the optic nerve head, as a result of which the capillaries lose some of their support. In this vulnerable state they collapse under the abnormal intraocular pressure. Thus the hypothesis does not deny that ischaemia is involved, but suggests that the levels of intraocular pressure commonly found in chronic simple glaucoma would not be high enough to produce damaging ischaemia without the initial factor of loss of glial support to the capillaries.

Lynn tackles the problem of how to explain arcuate scotomata, passing smoothly from temporal to nasal quadrants, in terms of the arrangement of nerve fibres at the optic nerve head. His diagrams give a lucidity of explanation which could hardly be achieved verbally.

These examples are quoted to indicate the level of interest to be found in all the sections. Anyone who looks after glaucomatous patients is bound to find something stimulating and helpful in this book. J. GLOSTER

Vitrectomy: A Pars Plana Approach. By R. MACHEMER. 1975. Pp. 136, 87 figs, refs. Grune & Stratton, New York (price not given)

This excellent book presents the author's personal experience, based on over 500 vitrectomies. The emphasis is on vitrectomy technique, rather than on the evaluation of indications and results.

The first chapter describes in great detail the VISC itself, the viewing system, and illuminating system. The second chapter deals briefly with the selection of patients and preoperative evaluation. Special emphasis is placed on the value of the bright-flash ERG and ultrasound in the preoperative examination of patients with vitreous opacities. The third chapter gives a detailed description of surgical techniques and complications. The four basic movements of the VISC are described and then the more complicated manoeuvres dealing with the peeling of epiretinal membranes in cases of massive periretinal proliferation; the treatment of giant retinal tears by intraocular gas tamponade is described in detail. The fourth chapter deals with the postoperative period. The brief appendix written by W. E. Benson is designed to help the beginner by practising on rabbits' eyes.

Dr Machemer emphasizes that pars plana vitrectomy is not an easy technique to learn and should be reserved for those who intend to specialize in this type of surgery. This book is highly recommended for all ophthalmologists, particularly those who are contemplating on embarking on this most exciting and challenging field of eye surgery. J. J. KANSKI

Brit. J. Ophthal. (1976) **60**, 490

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Eye-Bank Association of America, Inc.

Las Vegas, 5 *October* 1976

The scientific programme will now be held from 9.0 am to 12.30 pm (not as previously announced in the afternoon) at the Aladdin Hotel, Las Vegas, Nevada.

For further information write to R. D. Richards, MD, Department of Ophthalmology, University of Maryland Hospital, Baltimore, Maryland 21201, USA.

Third International Corneo-Plastic Congress

London, 29 *June to* 1 *July* 1977

This will be held at the Royal Festival Hall in London. Further details may be obtained from T. A. Casey, FRCS, Corneo-Plastic Unit, Queen Victoria Hospital, East Grinstead, Sussex.

2nd World Congress in Ergophthalmology

Stockholm, 13 *to* 16 *June* 1977

The International Society of Ergophthalmiology announces the 2nd World Congress of Ergophthalmology to be held at the Karolinska Institute, Stockholm. Symposia will be held on ocular hazards to electromagnetic radiation, mechanical hazards to the eye, chemical eye injuries, and vision requirements in work; free papers are also invited. For further information write to Anders Hedin, MD, General Secretary, Department of Ophthalmology, Karolinska Sjukhuset, S-104 01 Stockholm 60, Sweden; or Ergophthalmology 77, Stockholm Convention Bureau, Strandvägen 7 c, S-114 56 Stockholm, Sweden.

International Congress of Neurogenetics and Neuro-ophthalmology

Nijmegen, 8 *to* 10 *September* 1977

The main subjects to be discussed at the fifth congress are: myasthenia, microspherophakia (subluxatio lentis), optic atrophies, and neuroretinal degenerations.

For further information write to August F. Deutman, Institute of Ophthalmology, University of Nijmegen, Philips van Leydenlaan 15, Nijmegen, The Netherlands.

The Jules Stein Eye Institute

Los Angeles, 12 *November* 1977

A seminar entitled Current Concepts in Ophthalmic Plastic Surgery will be held at Los Angeles, California. The co-chairmen will be Dr Henry Baylis and Dr David Kamin.

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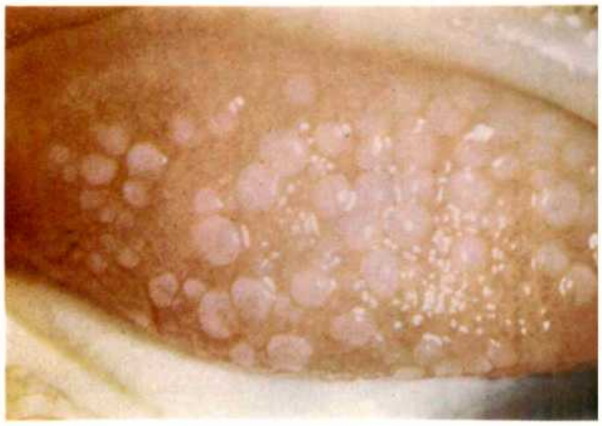
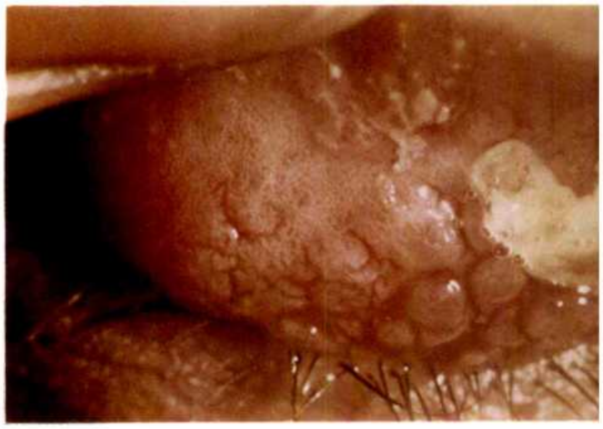
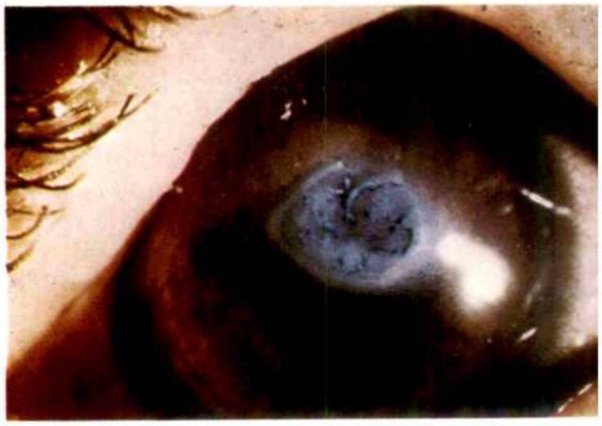


Right upper tarsus of adult patient with vernal kerato-conjunctivitis showing 'cobblestones' due to giant compound papillae.



Upper tarsal plate in active vernal disease. Note fine lace-like scarring and profuse mucopurulent discharge.



Indolent vernal corneal ulcer stained with alcian blue to demonstrate mucous deposition.

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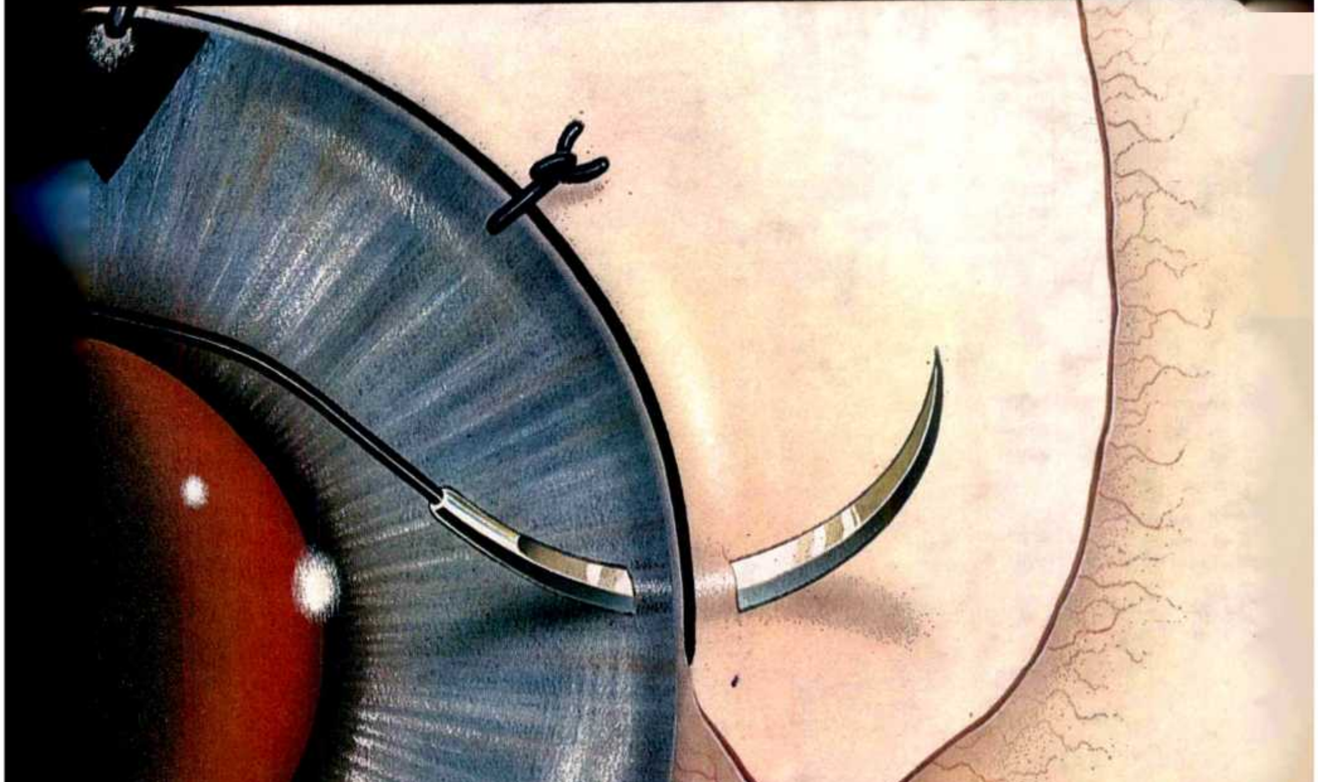

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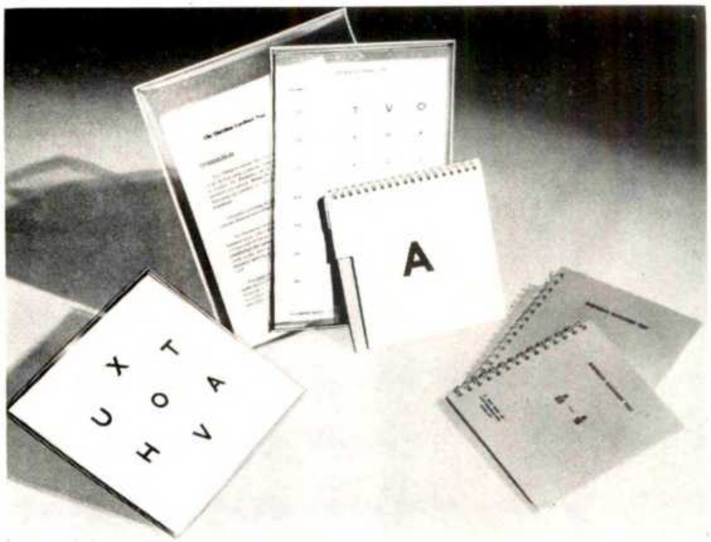

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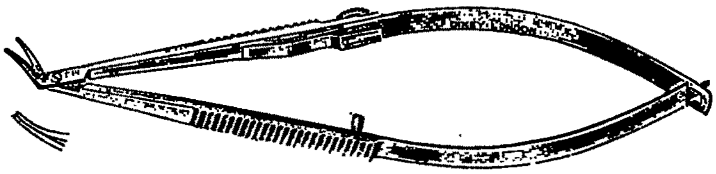

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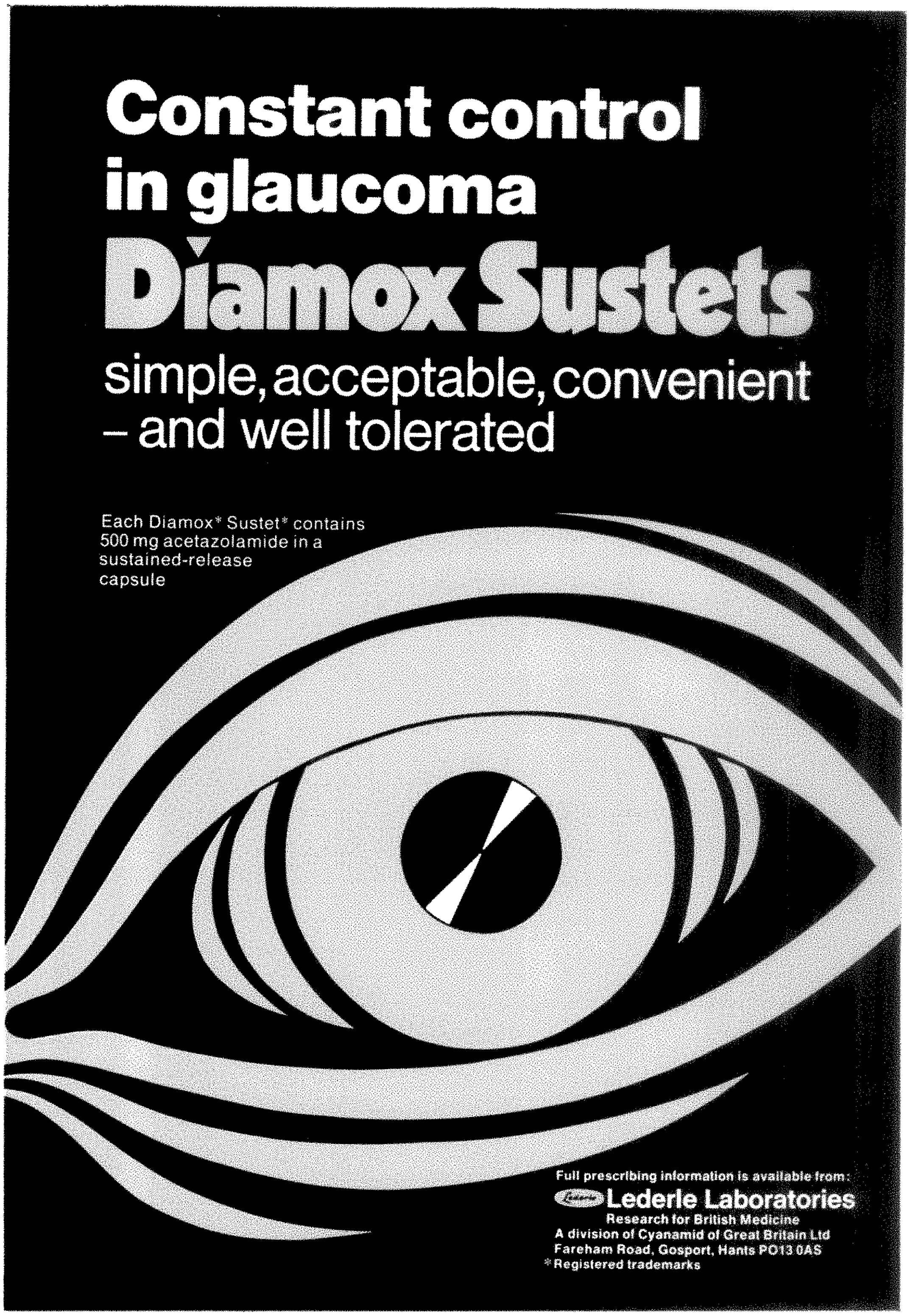

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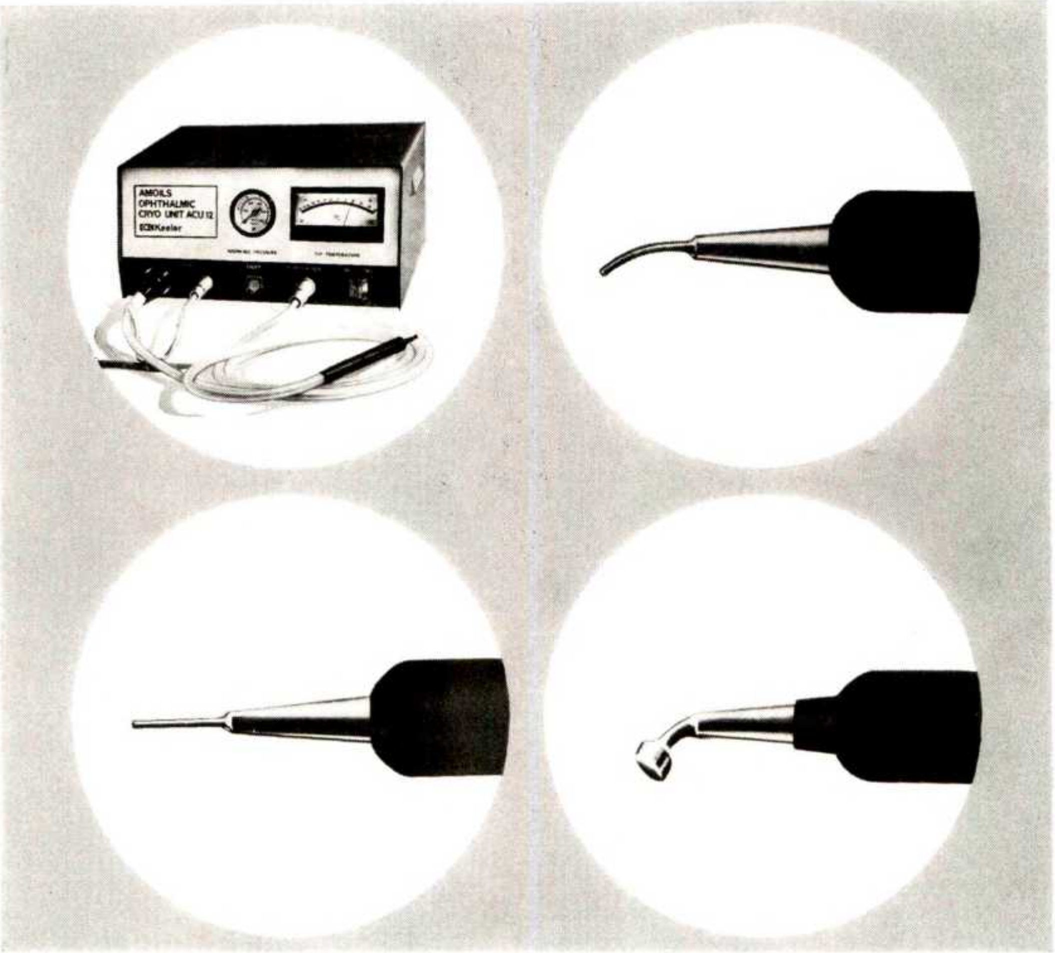

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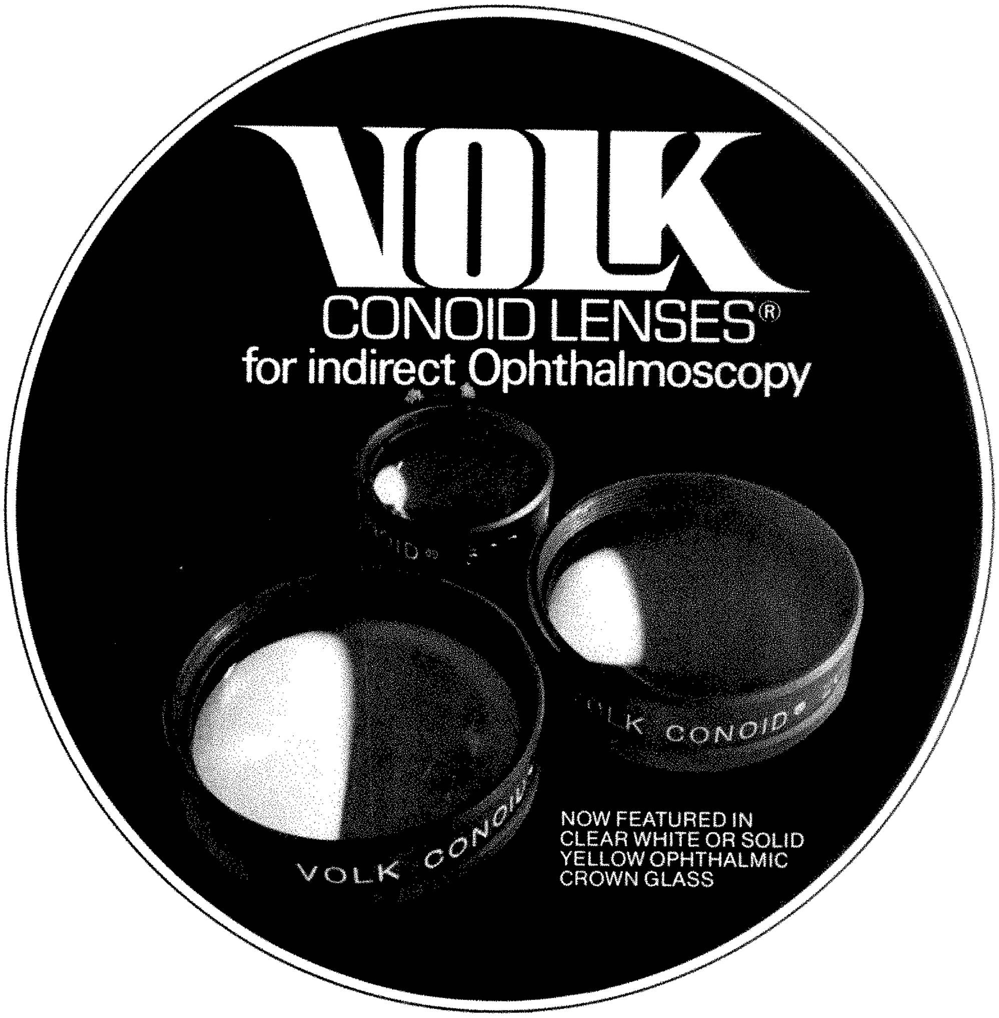
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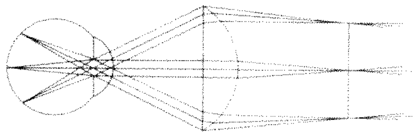

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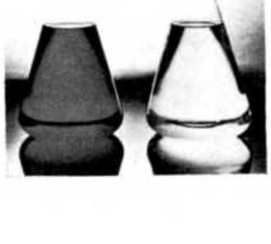

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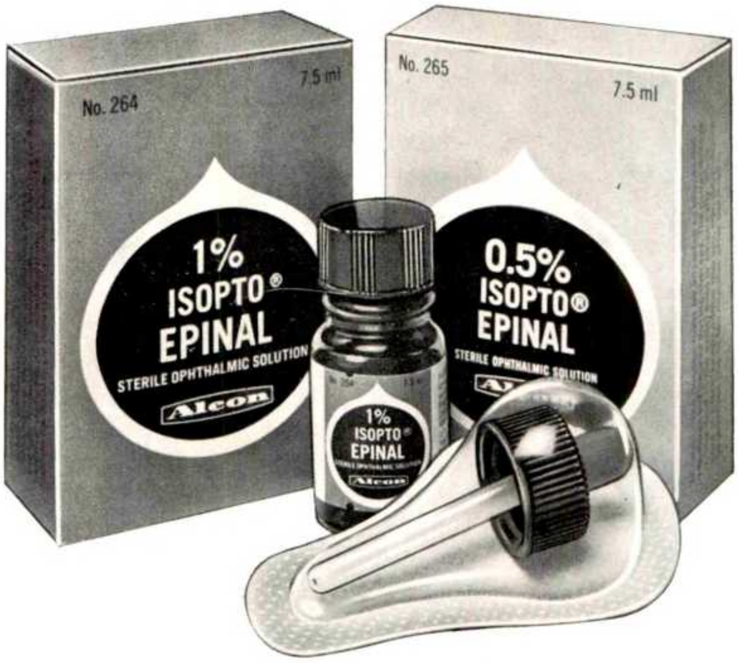

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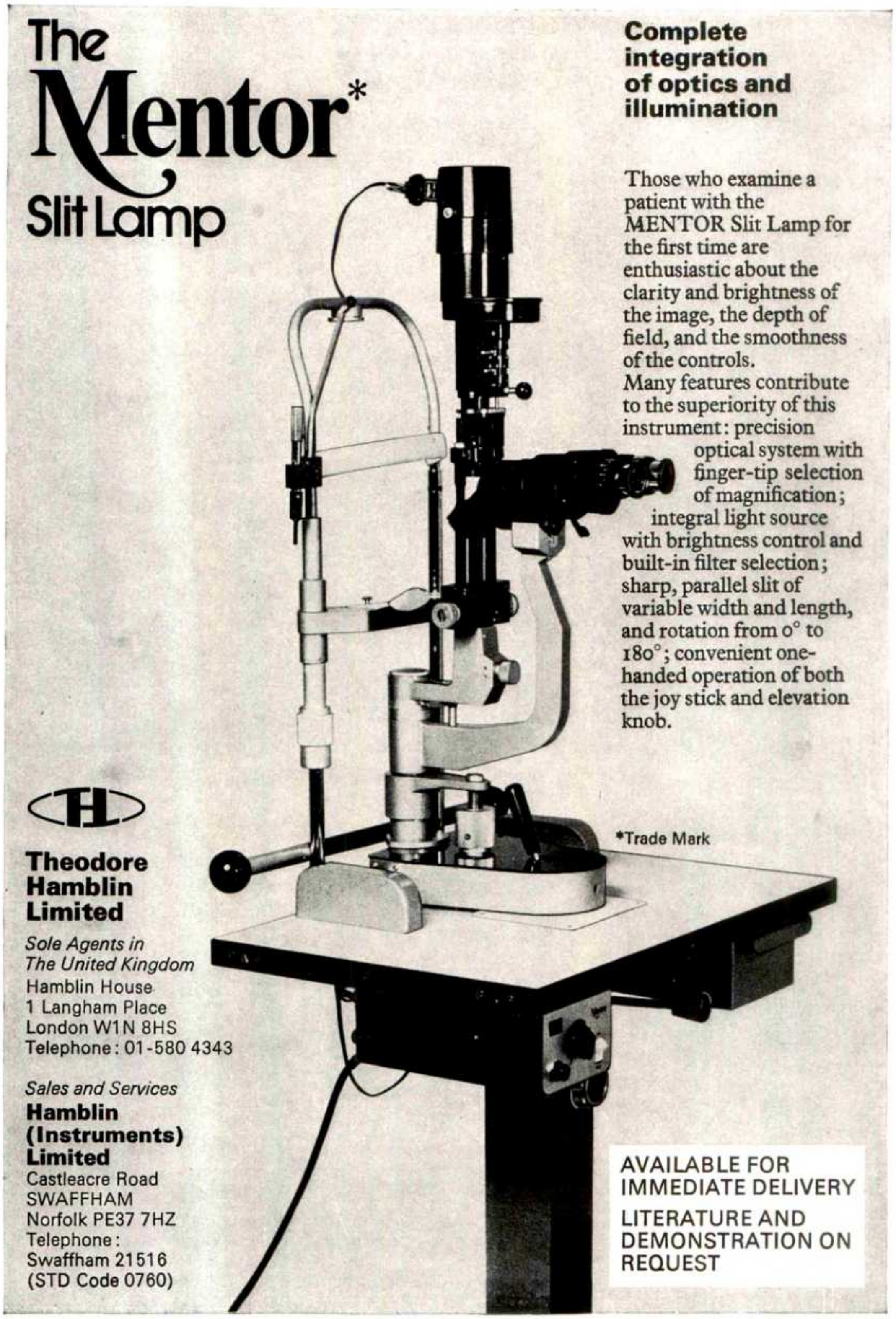

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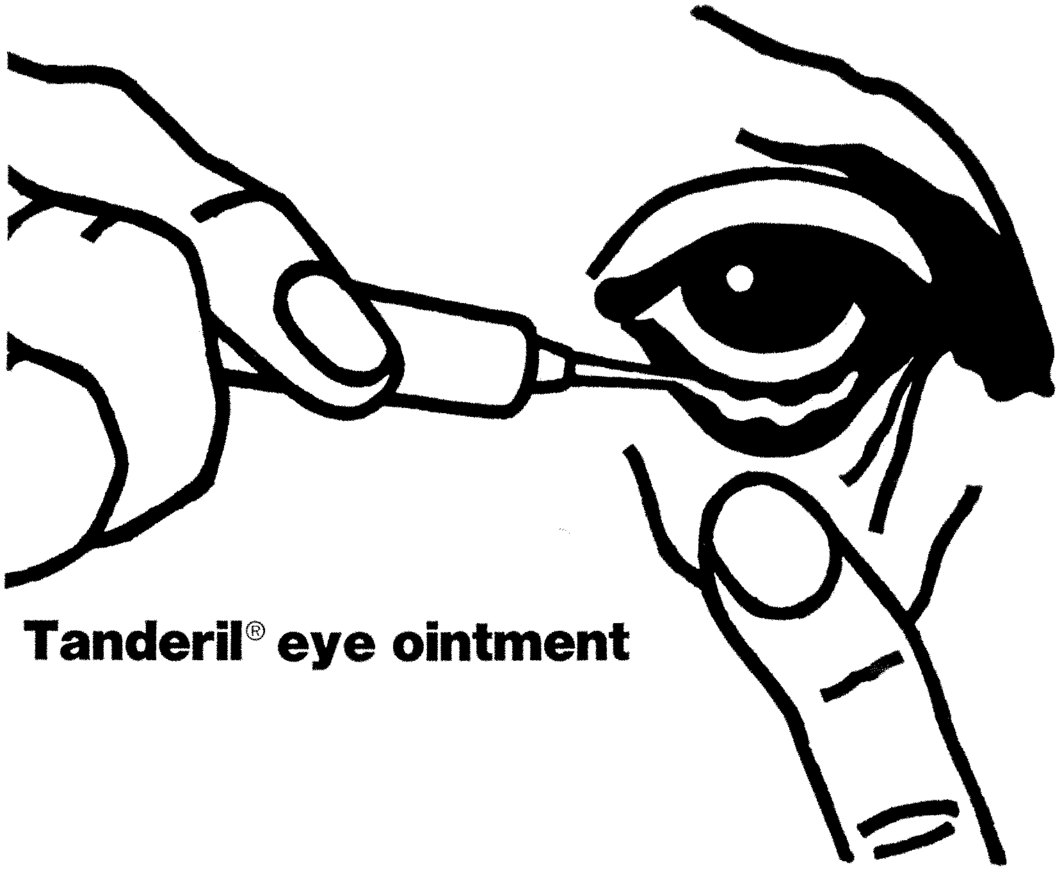

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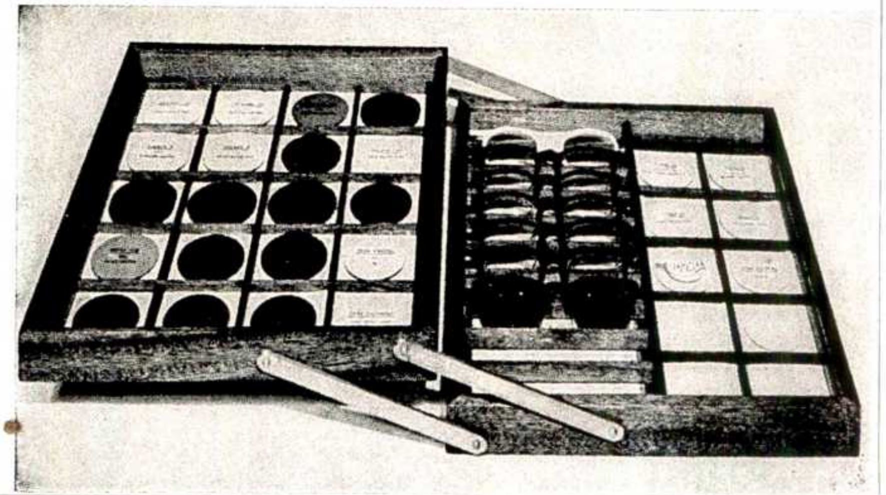

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Editorial: Hope for humanity in the Middle East

Communicable ophthalmia—the combination of trachoma and acute ophthalmia—remains today the most important cause of preventable blindness, some two million having succumbed out of five hundred million affected. In this WHO Blindness Year it is pertinent for the *British Journal of Ophthalmology* to publish a working paper which discusses the chronic trachomatous pathway to loss of sight and inseparably related pathway to blindness through acute ophthalmia. The problem is so defined in the first paper of this issue that lay-folk and administrators can readily understand the needless trail of devastation involved, grasp the importance of eradication of hyperendemic trachoma, and be encouraged to take part in the proposed programme of prevention and treatment.

The control of this age-long scourge calls for action by humanists and governments of all creeds and colours, it demands deeds not words, generosity not piety. In a world where medical science knows no boundaries, mankind is afforded once again an opportunity to demonstrate a unity of purpose and to forget, however briefly, its many differences.

Brit. J. Ophthal. (1976) 60, 492

Communicable ophthalmia: the blinding scourge of the Middle East

Yesterday, today and ? tomorrow

BARRIE R. JONES AND SOHRAB DAROUGAR
WHO Collaborating Centre for Reference and Research on Trachoma and Other Chlamydial Diseases, Department of Clinical Ophthalmology, Institute of Ophthalmology, Moorfields Eye Hospital, London
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Division of Ophthalmology, University of Texas, San Antonio, Texas, USA

Blinding and non-blinding trachoma

A year ago we introduced the concept that, from the public health point of view, trachoma should be divided into blinding trachoma and non-blinding trachoma (Jones, 1975). This concept has found a ready acceptance (Dawson, Jones, and Darougar, 1975) and has been of value in focusing attention on the urgent need for surveys in many countries to determine the presence and the magnitude of blinding trachoma.

Communicable ophthalmia

These surveys are the key to effective action but before considering them in detail it is necessary first to clarify the interrelations of trachoma: the classical chronic ophthalmia of chlamydial causation, and mucopurulent conjunctivitis (MPC), or acute ophthalmia, of bacterial causation. Both chronic ophthalmia (trachoma) and acute ophthalmia lie together within the single environmentally-determined complex entity that is well named 'communicable ophthalmia'.

'Ophthalmia' means inflammation of the eye; this is appropriate because it is the total lifelong load of chronic inflammation with acute exacerbations that yields the progressive harvest of needless blindness. 'Communicable' characterizes the essential nature of the Middle Eastern ophthalmia in that it is readily communicable from one individual to another. The conditions that lead to continuing massive pressure of communication of eye infection from one person to another are thus the roots of communicable ophthalmia and constitute the unifying factor shared by both the chronic and the acute ophthalmias.

Trachoma: a multicyclic infection in which pressure of infection determines severity of disease

Our observations in Iran indicate clearly that trachoma can be a multicyclic infection in which each cycle adds its quota of damage (Jones, 1975). The continuing pressure of re-infection in a community thus determines the severity of the disease and the ultimate degree of damage. The eye-seeking flies appear generally to provide the additional dimension to transmission of infection that escalates the pressure and the duration of exposure to infection into a life-long environmentally-determined programme of re-infection with *Chlamydia trachomatis* and the pathogenic ocular bacteria, thereby producing the mass blinding scourge: blinding hyperendemic trachoma which is the central core of communicable ophthalmia (Fig. 1).

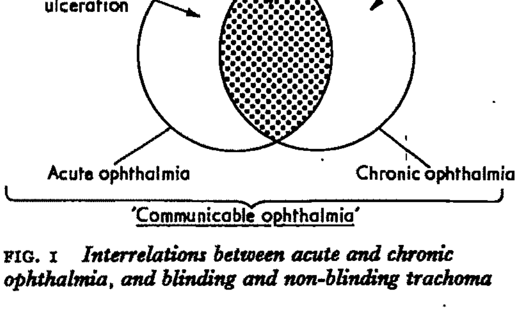


FIG. 1 *Interrelations between acute and chronic ophthalmia, and blinding and non-blinding trachoma*

Presented as a working paper to the World Health Organization Interregional Meeting on the Prevention of Blindness in Baghdad, Iraq, 29 March to 1 April 1976

Address for reprints: Professor B. R. Jones, Department of Clinical Ophthalmology, Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

The role of flies in communicating ophthalmia

It has long been accepted that flies provide the main route of transfer of infection in the seasonal epidemics of bacterial conjunctivitis in the Middle East (Wilson, 1936) and in similar climatic zones of Africa and Australia where trachoma is at its worst. Our current studies in southern Iran have shown that the discharges from eyes and noses may contain viable *C. trachomatis*. By means of fluorescein tracing we have shown that such material is transferred in a barrage of fly-vomits to the eyes and nares of adjacent children in a matter of minutes, and we have grown *C. trachomatis* from the flies caught around these children's eyes (Fig. 2).

Acute ophthalmia overshadows and may mask the presence of active trachoma. In a study of acute ophthalmia, in collaboration with Professor M. Khalaf Al-Hussaini and his staff in the Hospital of the University of Assyout in Upper Egypt during November 1975, we demonstrated, by the micro-immunofluorescence test, the presence of antibody to *C. trachomatis* in the tears at 1/8 or greater titre in 18·6 per cent of 124 children under eight years of age presenting with acute ophthalmia. The antibody was to type A in 78·2 per cent; B in 13 per cent; C in 4·4 per cent and D/E in 4·4 per cent. This provides evidence of simultaneous infective trachomatous disease.

'Communicable ophthalmia'

We therefore see 'communicable ophthalmia' as a single, but complex entity consisting of two clinically and microbially discernible sections: mucopurulent conjunctivitis or acute ophthalmia, and trachoma or chronic ophthalmia that develops into blinding trachoma in the overlapping epidemiological conditions that lead also to epidemics of acute ophthalmia (Fig. 1).

Blinding hyperendemic trachoma, the overlapping core of communicable ophthalmia, is thus an environmentally-determined menace resulting from life in communities with open faecal and rubbish disposal, poor personal hygiene, and short interpersonal distance in climates favourable to the production of a high density of the synanthropic eye-seeking flies: *Musca domestica* and *Musca sorbens*, the latter breeding selectively in human faeces.

Laboratory models of environmentally-determined programmes of infection

The validity of these epidemiologically-derived concepts is being confirmed in our laboratory using animal models of the environmentally-determined programme of re-infection and mixed infection. Dr Marjorie Monnickendam and Dr Sohrab Darougar have shown that after the third re-infection of guinea-pigs with the guinea-pig inclusion conjunctivitis (GPIC) chlamydial agent, this normally benign disease develops much more severe inflammation with conjunctival cicatrization resembling trachoma.

Dr Hadi El Sheikh and Dr Sohrab Darougar have shown in cats that bacterial infection with streptococci alone causes only a mild, short-lived mucopurulent conjunctivitis. Infection with the feline chlamydial keratoconjunctivitis agent alone causes a chronic trachoma-like infection with pannus and conjunctival scarring. Mixed infection with both agents, however, produces a much more severe disease with rapidly blinding ophthalmia in half the cats (Jones, 1975).

Surveys for preventable blindness from communicable ophthalmia

These newly defined concepts make it clear that all countries that have, or suspect that they may have, problems of blindness from communicable ophthalmia, need urgently to carry out surveys of suspected rural communities. The recommended methods have been set out by Dawson and others (1975). It is essential that the full age range of the population be surveyed by means of a valid random sample. Thus all ages must be surveyed for: corneal blindness, potentially blinding trachomatous deformities of the lids (Jones, Barras, Hunter, Darougar, and Mohsenine, 1976), and for severe grades of intensity of upper tarsal conjunctival inflammation.

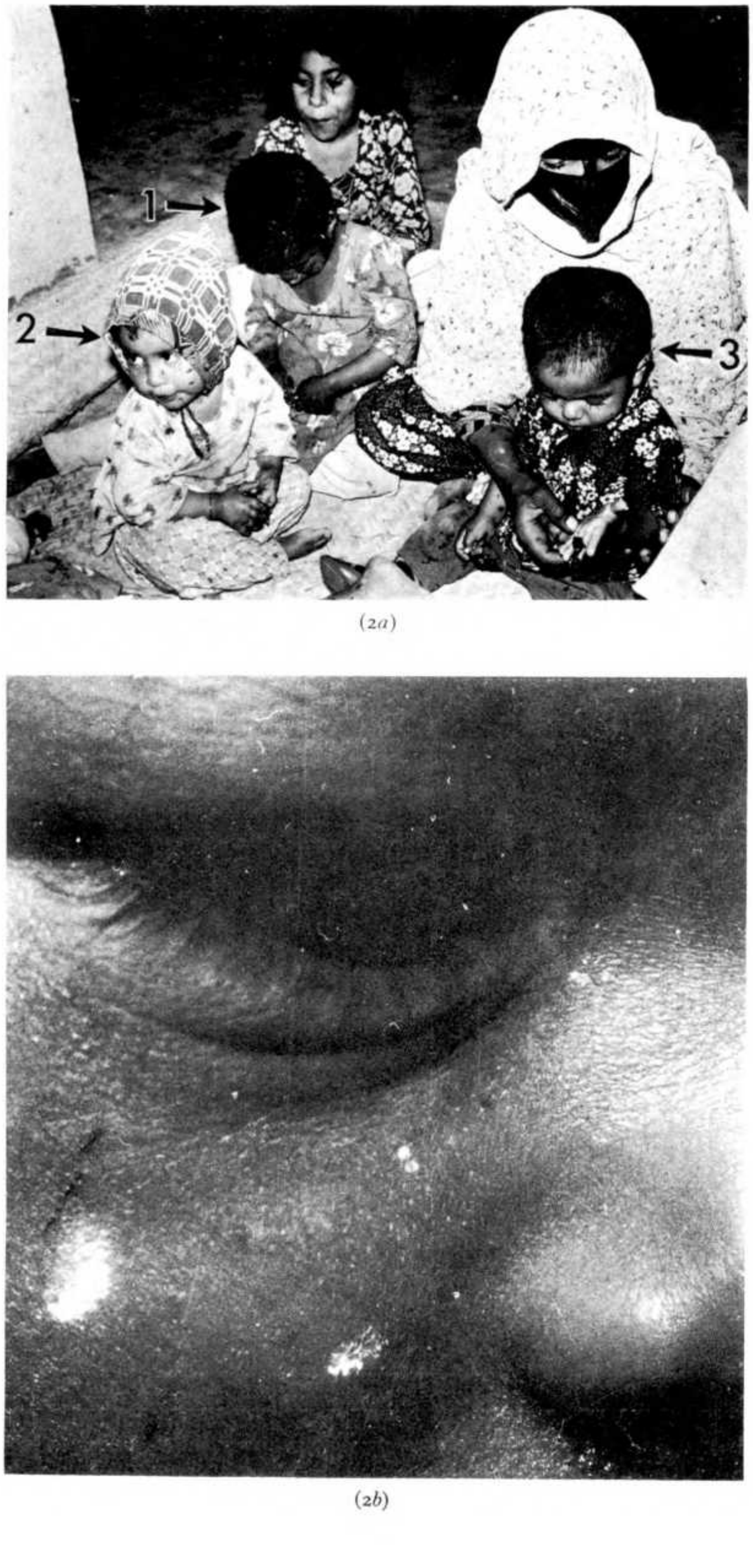
CORNEAL BLINDNESS

Corneal blindness comes progressively with age from trachoma whereas it comes suddenly from corneal ulceration complicating acute ophthalmia, strikingly in the young, but also in the old, especially those with trachomatous deformities of the lids.

POTENTIALLY BLINDING TRACHOMATOUS DEFORMITIES OF THE LIDS

The potentially blinding abrasive trachomatous deformities of the lids—trichiasis and entropion, or notching of the lid margin or other defects of lid closure resulting from subconjunctival fibrosis of the levator causing functional shortening of the lid (Jones and others, 1976)—are greatly aggravated if scarring has also caused xerosis by occluding the lacrimal ductules in the fornix, or if there is reduced corneal sensation.

These deformities of the lids keep eyes sticky,



(2*a*)

(2*b*)

FIG. 2* (a) *Fly-borne transmission of ocular discharges within a pool of ocular promiscuity. Fluorescein placed in the eye of Child* 1 *transmitted by fly vomits to the eyes of Child* 2 *and Child* 3 *within* 20 *and* 40 *minutes* (b) *Child* 2—*Fluorescing spots of fly vomit photographed in blue light through a yellow filter, indicating fly-borne transmission of conjunctival discharge from Child* 1 *within a period of* 20 *minutes. Fluorescein was also present in the tear film of both eyes of both children*

*Reproduced by permission of the *Trans. ophthal. Soc. U.K.*—Jones, B. R. (1975)

thereby making them a prime target for flies, thus holding the adult person in the infant pool of ocular promiscuity (Jones, 1975), and committing the individual to an environmentally-determined life-long programme of re-infection. Blindness is thus likely to ensue from relentless progression of trachoma, with the mixed chlamydial and bacterial load causing severe inflammation and scarring, aggravated by the physical trauma of trichiasis. Alternatively, blindness can ensue from acute ophthalmia complicated by corneal ulceration to which these eyes are especially liable. The trachomatous lid deformities thus play a determining role in both the chronic trachomatous and in the acute bacterial pathways to blindness.

To block this relentless progression requires immediate preventive action, continuing surveillance, and the maintenance of primary eye health care. The immediate preventive action requires the identification of individuals at risk and the provision of surgical correction and medical therapy. This should be accompanied by measures to reduce the pressure of re-infection by means of mass chemotherapy of the reservoir of infection in the community, especially in pre-schoolchildren and other young people. Reduction in the factors for transmission of infection, by means of personal and community sanitation, should also be of particular benefit to those at high risk because of lid deformities; but no measurements of this effect have been made.

Individuals with lid deformities require continuing surveillance for recurrence of trichiasis, and the community requires surveillance for recrudescence of transmission of infection. They are also the adults most likely to need good primary eye health care: immediate treatment of ophthalmia or the emergency care of corneal ulcers.

INTENSITY OF CONJUNCTIVAL INFLAMMATION

The survey will also reveal the (frequently unrecognized) prevalence of severe conjunctival inflammation that reflects a high pressure of transmission of infection. This requires mass chemotherapy of all infected persons, or at least of all those with moderate or severe grades of intensity of inflammation (Dawson and others, 1975). Some programmes may compromise and settle for delivery only to schoolchildren. However, Fig. 3, showing the age and sex distribution of active trachoma in the village of Sar Rig in southern Iran, indicates just how illogical and suboptimal is the delivery only to the five- to 15-year age range. In many communities this would also restrict delivery to the more favoured children of the more favoured families.

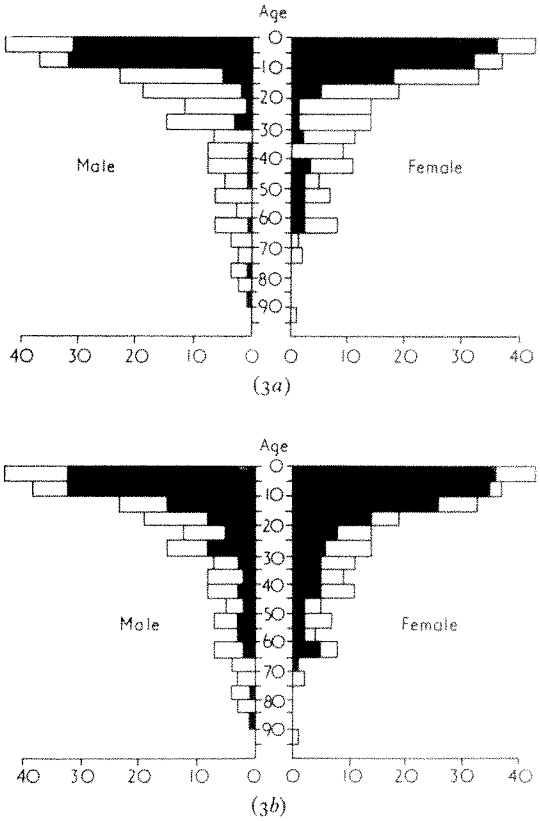
Mass chemotherapy for control of communicable ophthalmia

MASS ANTIBIOTIC PROGRAMMES

The WHO-recommended scheme of mass topical intermittent chemotherapy consists of the administration of a tetracycline eye ointment to both eyes once, or preferably twice, a day for five days each month for three, or preferably six, months. This is known to have an impact and, at present, should form the basis of mass control programmes.

OCULAR THERAPEUTIC SYSTEMS AND ORAL CHEMOTHERAPY

Other methods of delivering chemotherapy are, however, under investigation. Continuous delivery ocular therapeutic systems of poor retention in children have been shown to be at least as effective as twice daily ointment regimens (Jones, 1975).



(3*a*)

(3*b*)

FIG. 3* *Active trachoma* (a) *upper tarsal and* (b) *in whole conjunctiva, in right eye in total population, by five-year age groups and sex, in Sar Rig,* 1972

*Reproduced by permission of the *Trans. ophthal. Soc. U.K.*—Jones, B. R. (1975)

Improved devices with much better retention may have a great deal to offer.

Long-acting oral tetracycline chemotherapy has potential advantages in terms of ease, certainty, and continuity of delivery (Jones, 1974, 1975). The possibility of large-scale control of trachoma by the community-based administration of a single short course of, say, three weeks of three oral doses a week of doxycycline (5 mg/kg), is shown by the persisting effect still strikingly apparent in the village of Sar Rig in southern Iran two years after a course of six such doses given only twice-weekly for three weeks, two years earlier. In that case the three-week oral treatment was given to all persons with moderate or severe conjunctival inflammatory disease; approximately half of them had previously received intermittent monthly treatment with either oxytetracycline eye ointment twice a day for one week each month, or single monthly doses of doxycycline (5 mg/kg) for one year.

The Table indicates that before oral chemotherapy, 25 per cent of the population (427) had grade 3 or 4 (moderate or severe) upper tarsal conjunctival inflammatory disease, despite earlier intermittent treatment. The three-week oral chemotherapy was given in November 1973. When the whole population, less deaths and emigrants, but including new births and immigrants, was examined one year after chemotherapy, the figure had been reduced to 12 per cent. At a two-year follow-up the preliminary figures showed 9 per cent. Examination of absentees will probably reduce this figure. It should be noted that these figures show prevalences in the whole population, including new births and new arrivals, not only in those who were treated among whom there was a lower prevalence of active disease.

Table *Persistence of effect of a single period of three weeks' oral chemotherapy (doxycycline 5 mg/kg twice a week, i.e. six doses) in November 1973 to all persons in Sar Rig, Bandar Abbas, southern Iran, with grade 3 or 4 intensity of trachomatous conjunctival inflammation, after earlier intermittent monthly topical oxytetracycline, or systemic doxycycline, treatment in approximately half the cases*

		Examination					
		Whole eye (per cent)			*Upper tarsal (per cent)*		
Date	*No. persons examined*	*Grade* 3	*Grade* 4	*Grade* 3 + 4	*Grade* 3	*Grade* 4	*Grade* 3 + 4
November 1972 (before treatment)	427	20	8	28	15	10	25
February 1975 (1 year after treatment)	396*	6	8	14	2	10	12
February 1976 (2 years after treatment)	375*†	5	5	10	3	6	9

*Whole population including new births and arrivals not treated in 1973

†Data on absentees to come, mainly adults working elsewhere

Much remains to be done before this could be recommended for widespread use, but these preliminary results indicate that such a course of chemotherapy can reduce the reservoir of infection to a level at which, in present environmental conditions, transmission of infection is controlled for an encouragingly long period. The full results with findings in the adjacent control village will be published elsewhere.

Expected effects on trachoma and acute ophthalmia

Within the complex, communicable ophthalmia, it is likely that trachoma is easier to control by chemotherapy than may be the case for acute ophthalmia. Trachoma, being a chronic infection, waits for the delivery of chemotherapy whenever that is delivered. Acute ophthalmia, on the other hand, comes and goes and does not wait. Topical chemotherapy programmes that control trachoma should ameliorate transmission and severity of acute ophthalmia; but they are not likely to eliminate the problem, which is therefore likely to persist in the villages, as it does in many of the urban populations of the Middle East. This requires the provision of primary eye care: immediate availability of antibiotic therapy of acute ophthalmia whenever required, and the emergency care of corneal ulcers.

However, real control of communicable ophthalmia should come from fly control. There is, therefore, an urgent need to converge resources of rural sanitational and agricultural technology, health education, and current developments in fly control to evolve effective, acceptable, long-term, low-cost methods of fly control.

MONITORING OF EFFECT OF CONTROL PROGRAMMES

Whatever the detail of the antibiotic programme, or other intervention, it is essential that control measures should include provision for monitoring the effect and efficiency of the intervention. This can be done by 'before and after' comparisons, and by simultaneous observations in untreated control communities. These should be followed by long-term follow-up of appropriate samples and the maintenance of long-term surveillance for recrudescence of transmission of infection. In each case the observations should include quantitative clinical data on the intensity of conjunctival inflammation, the presence of lid deformities, and the prevalence of corneal blindness. It is desirable that this be supplemented by data on the presence of *C. trachomatis* by direct demonstration of the agent, or by isolation, and by data on antibody levels to this agent in tears and sera (Jones, 1974).

ADMINISTRATION OF TRACHOMA CONTROL ACTIVITIES

Health Administrators should consider the general principle that in setting up single categorical disease control programmes such as are required for trachoma-communicable ophthalmia, the exercise should be planned as the first step in provision of primary rural (eye) health care, and not as an independent, indefinitely self-perpetuating organization. As trachoma comes under control the trachoma team, with skill in eye disease and community medicine, should integrate with the primary rural health care service, and provide primary eye care to contribute importantly in control of acute ophthalmia, and in maintaining surveillance as outlined above. The trachoma team, thus integrated in community medicine, must, however, maintain effective links with secondary urban ophthalmic care units, upon which it will be dependent for training, guidance, and the referral of patients. In this way, permanent careers could be provided, thus avoiding the loss of skilled manpower for primary rural health care.

Communicable ophthalmia: the blinding scourge

Communicable ophthalmia has certainly been the blinding scourge of the Middle East in the past. It is certainly a continuing problem of major importance in rural communities that are largely bypassed by economic development, as is the case in southern Iran (Jones, 1975). The future in such populations is in the balance. In the absence of economic development bringing major changes in sanitation and medical services, it will depend on governmental decisions and the correct implementation of effective action.

We see blinding trachoma and acute ophthalmia which together constitute 'communicable ophthalmia', as one of the greatest, but preventable, afflictions of mankind which has its roots in life in communities with open faecal and rubbish disposal, with poor personal hygiene in climates that favour high densities of the synathropic eye-seeking flies. Can we continue to allow such a harvest of needless blindness to persist, while throwing vast resources into increasingly expensive small-return areas of urban curative medicine? What country can afford indefinitely to neglect its rural population?

ACTION TO PREVENT BLINDNESS

We would urge action to prevent this needless blindness by carrying out surveys of under-served rural populations to determine the location of high risk communities and by implementing topical ocular chemotherapy programmes in these. At the same time, we would urge action to assess alternative chemotherapy, such as may be provided by continuous delivery ocular therapeutic systems or by oral chemotherapy. But, especially, we would urge action directed at the roots of the problem, to assess the practicability and efficacy of fly control by personal and community sanitation and by other means.

ACTION BY GOVERNMENTS

This demands action by governments. The implementation of large-scale surveys and chemotherapy programmes are clearly the responsibilities of governments. Research now needs to be integrated with governmental action. Research in this field of prevention of blindness falls into three phases. The first has concerned case studies, work with animal models, and clinical trials of therapy. This has been done by universities with support from grant-giving bodies.

The second phase concerns field studies, work with animal models of the environmentally-determined human ecology, and field trials of therapy. This is being done by universities and supported by internationally orientated grant-giving bodies. Knowledge accumulated from these studies now requires the third phase to begin: namely, operational research at the pilot control programme scale, to compare various methods of control, to make measurements of cost and effect, and not to shrink from attempting to tackle the roots of the problem. This clearly requires the collaboration of national administrations for health, universities with support by international agencies, and governments.

LACK OF STAFF, CAREERS AND TRAINING FACILITIES FOR PREVENTIVE WORK IN EYE DISEASE

If action to halt this needless blindness is decided upon, the choice of what to do is reasonably straightforward. But the implementation may be delayed by lack of knowledge of clearly defined rural health technology, and by shortage of staff trained for preventive work in eye disease, both at medical and ancillary levels.

Osler epitomized the sense of this obstacle in his comments about the medical teachers of his time: '*Cabin-cribbed, confined within the four walls of a teaching hospital, practising the cloistered virtues of* *clinical medicine, how can they train men for a race of dust and heat, of which they know nothing?'*

To bridge this gap, and to help to meet this need 'It is proposed to establish in London a centre for training, recruitment, and research in public health ophthalmology and communicable eye disease, . . . with the immediate objective of making a substantial impact on the major problems of preventable rural world blindness'.

There is an urgent need for financial support for the establishment of such academic centres in preventive ophthalmology to ensure exposure of trainees to the challenges of community ophthalmology, and to encourage the recruitment of persons of high calibre into this field by the provision of attractive career posts in this work.

It is a pleasure to acknowledge the encouragement of Professor Ch. Mofidi, Professor M. A. Faghih, and Professor A. Nadim of the School of Public Health, Teheran, and for the arrangements that they and Dr A. Abrishemi, Ministry of Health, Bandar Abbas, have made for the work in a collaboration between the School of Public Health, the Ministry of Health, and the Institute of Ophthalmology, London.

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Retinal vascular changes in congenital hypertrophy of the retinal pigment epithelium

P. E. CLEARY, Z. GREGOR, AND A. C. BIRD
From Moorfields Eye Hospital and the Institute of Ophthalmology, London

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a well-defined clinical entity which is usually an incidental finding during routine fundus examination (Buettner, 1975). Recent reports have emphasized the characteristic features that distinguish it from malignant melanoma of the choroid and other pigmented fundus lesions (Buettner, 1975; Purcell and Shields, 1975). Stereoscopic fundus photography and fluorescein angiography are useful in confirming the diagnosis (Buettner, 1975). The histopathology is that of hypertrophy of a single layer of retinal pigment epithelial cells with an increase in the concentration of pigment granules within the cells, but whether this pigment is lipofuscin or melanin it has not been established (Kurz and Zimmerman, 1962; Buettner, 1975). The photoreceptor cells overlying the hypertrophic pigment epithelium degenerate and disappear, thus providing a morphological basis for accompanying visual field defects (Kurz and Zimmerman, 1962; Buettner, 1975). Intraretinal pigment migration is present in a minority of cases, but other abnormalities of the inner retina have not been previously identified. This report presents five cases with abnormalities in the retinal vasculature overlying areas of CHRPE.

Patients

The patients' ages ranged from 42 to 64 years. None had evidence of previous or other ocular disease. All were examined for signs of systemic disease but no abnormalities were found. Routine investigations were within normal limits and included a full blood count, chest *x*-ray examination, and electrocardiogram.

Clinical findings

OPHTHALMOSCOPY

The fundus lesions were solitary, round, flat, hyperpigmented, and well demarcated. They varied in colour from greyish-brown to black and in size from 1 to about 8 disc diameters. Characteristic lacunae were present in all, and the typical hypopigmented haloes surrounded four lesions. Abnormalities of the overlying retinal vessels were seen in only two cases, with gross attenuation of a retinal artery in one and sheathing of a vein in another. A discrete, hyperpigmented and slightly raised area about 1 disc diameter in size was observed in the centre of the lesion in one case (Fig. 1).

FLUORESCEIN ANGIOGRAPHY

Overlying retinal vascular abnormalities were demonstrated in all the lesions. In one there was no perfusion of the overlying retinal vessels (Fig. 2) and in another perfusion was absent except for delayed filling of a single retinal vein with late staining of its wall (Fig. 3). Gross attenuation of a retinal artery and its branches occurred in the centre of the lesion in one patient (Fig. 4). The remaining two patients gave a complicated appearance of retinal capillary closure with leakage of fluorescein from abnormal capillaries. In one leaking retinal capillaries and venules in the centre of the lesion were related to areas of retinal capillary closure or were present at the edge of non-perfused retina (Fig. 5). In the other an abnormal leaking capillary network corresponded to a hyperpigmented raised area in the centre of the lesion (Fig. 1). This capillary network filled in the earliest stages of the fluorescein angiogram when the surrounding retinal vessels were not perfused, thus implying an arterial supply from the choroid.

VISUAL FIELDS

Four patients were examined by Tubingen perimetry. In all four absolute scotomas corresponded to the site of the fundus lesions.

Discussion

The fundus lesions in these five patients correspond with previous descriptions of congenital hypertrophy of the retinal pigment epithelium (Reese and Jones, 1956; Reese, 1960; Kurz and Zimmerman, 1962; Hogan and Zimmerman, 1962; Buettner, 1975; Purcell and Shields, 1975). However, abnormalities of the overyling retinal vasculature have not before been identified. Retinal blood vessels have been described particularly as undeviated and normal (Buettner, 1975). The vascular

Address for reprints: P. E. Cleary, Moorfields Eye Hospital, City Road, London EC1V 2PD

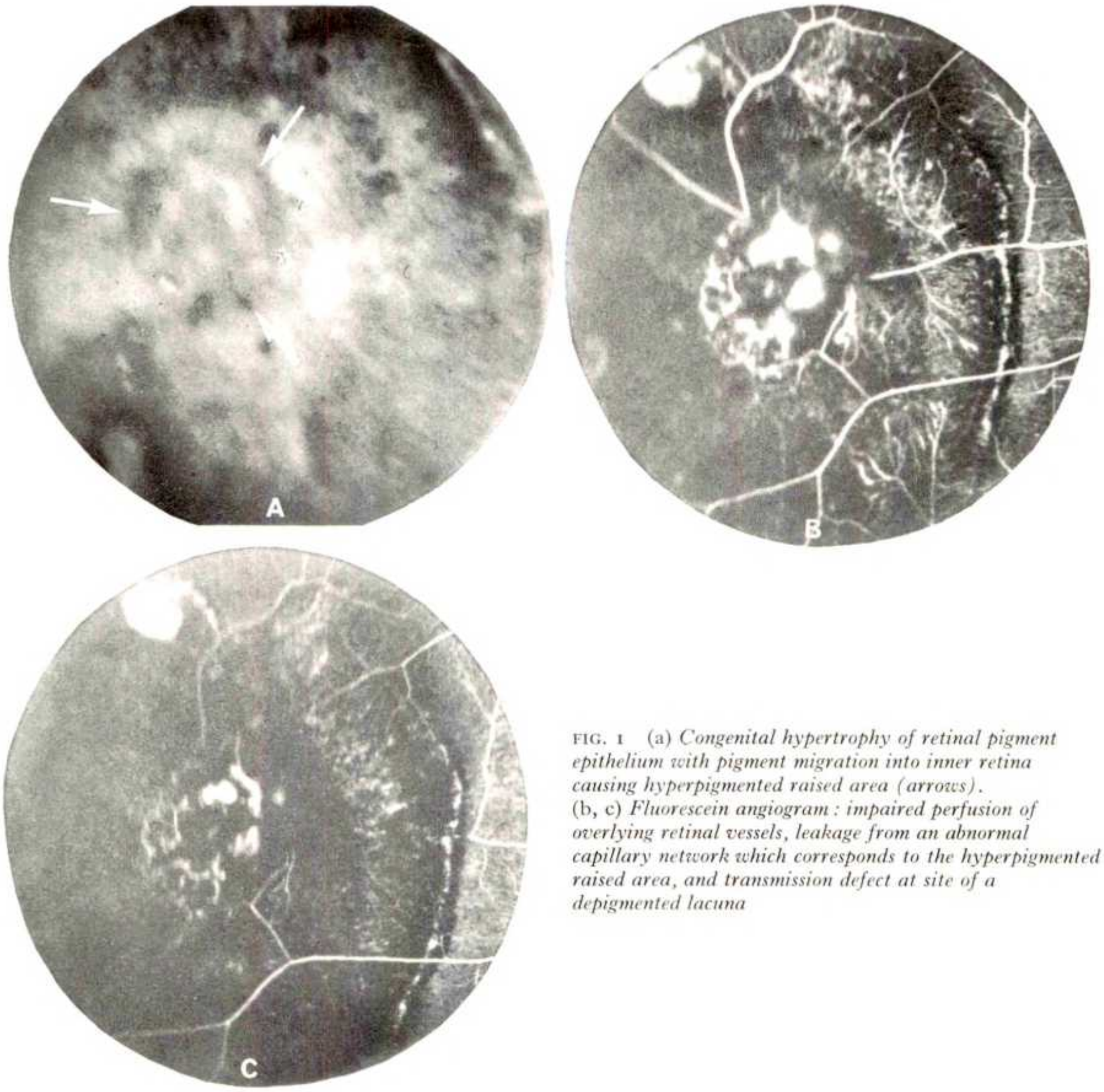

FIG. 1 (a) *Congenital hypertrophy of retinal pigment epithelium with pigment migration into inner retina causing hyperpigmented raised area (arrows).* (b, c) *Fluorescein angiogram: impaired perfusion of overlying retinal vessels, leakage from an abnormal capillary network which corresponds to the hyperpigmented raised area, and transmission defect at site of a depigmented lacuna*

changes in all our cases were defined by fluorescein angiography and consisted of vascular non-perfusion with obliteration of the retinal capillary bed. In addition, two cases had retinal capillary leakage, which in one was from presumed intraretinal new vessels. The configuration of the leaking capillary network in this second case (Fig. 1) suggested that the blood vessels were derived from the choroid. The associated pigment migration into the inner retina may well have been accompanied by fibrovascular ingrowth from subretinal tissues.

Photoreceptor degeneration in CHRPE is probably progressive, since the consequent visual field loss becomes denser with increasing age (Kurz and Zimmerman, 1962; Buettner, 1975). By contrast, the inner retina remains well preserved. The absolute scotomas demonstrated by Tubingen perimetry indicate that there was severe receptor cell loss in these patients with obliteration of overlying retinal capillaries.

Precisely similar retinal vascular abnormalities have been described in retinitis pigmentosa (Duke Elder, 1967; Noell, 1953), in the retinae of rats with hereditary visual cell degeneration (Gerstein and Dantzker, 1969), in light-damaged rat retinae (Dantzker and Gerstein, 1969), and after argon and ruby laser photocoagulation of monkey retinae (Okisaka, Kuwabara, and Aiello, 1975), in which

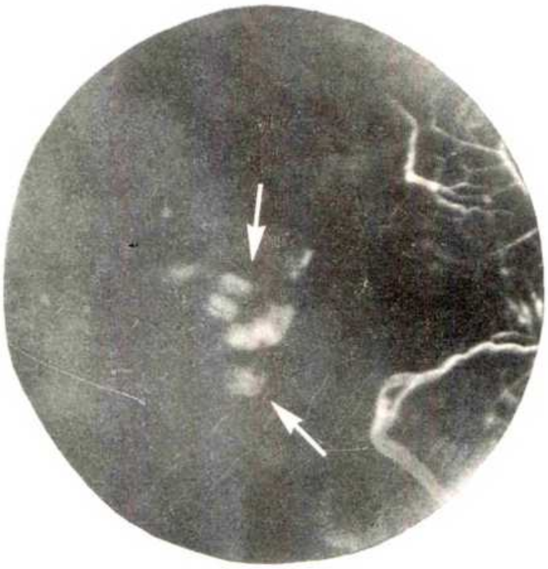

Fig 2

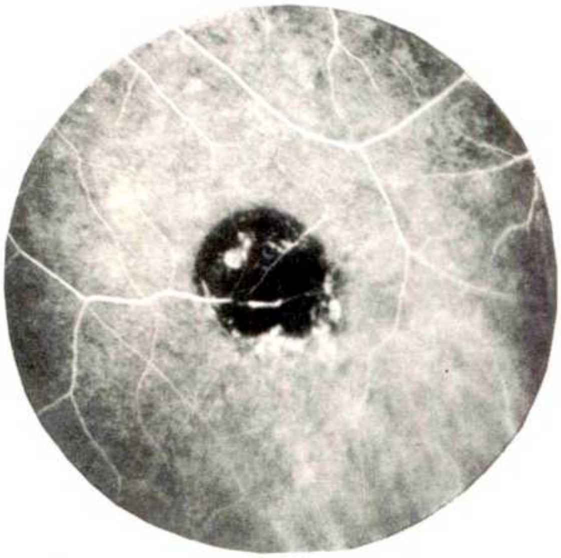

Fig 4

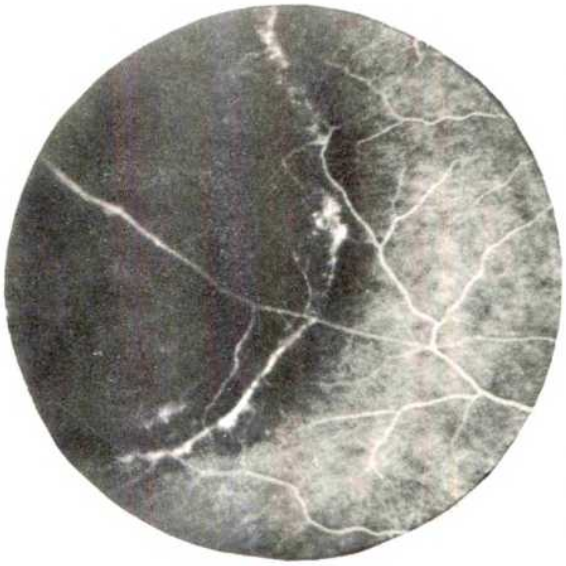

Fig 3

FIG. 2 *Fluorescein angiogram of congenital hypertrophy of retinal pigment epithelium showing no perfusion of overlying retinal vessels but with transmission defects at site of depigmented lacunae (arrows)*

FIG. 3 *Fluorescein angiogram of congenital hypertrophy of retinal pigment epithelium: no perfusion of overlying retinal vessels except for filling of a single vein*

FIG. 4 *Fluorescein angiogram of congenital hypertrophy of retinal pigment epithelium with attenuation of a retinal artery and its branches, typical lacunae, and hyperfluorescent lower border*

conditions there is combined degeneration of photoreceptors and retinal pigment epithelium. Obliteration of retinal capillaries was also observed in cats' eyes when iodoacetate was used to destroy selectively the photoreceptor layer alone, indicating that the presence of an intact retinal pigment epithelium did not seem to modify the vascular response to outer retinal atrophy (Dantzker and Gerstein, 1969).

In some of these conditions obliteration of retinal capillaries might possibly result from secondary changes in the inner retina after outer retinal atrophy, and in light-damaged rat retinae the most severe vascular changes coincided with considerable distortion of the inner retinal layers (Dantzker and Gerstein, 1969). However, these authors observed that the early stages of vascular degeneration preceded inner layer disease and they noted a close temporal relationship between the progressive degeneration with thinning of the outer retinal layers and the disappearance of retinal capillaries. They concluded that retinal capillary degeneration occurred as a result of outer retinal loss and was not

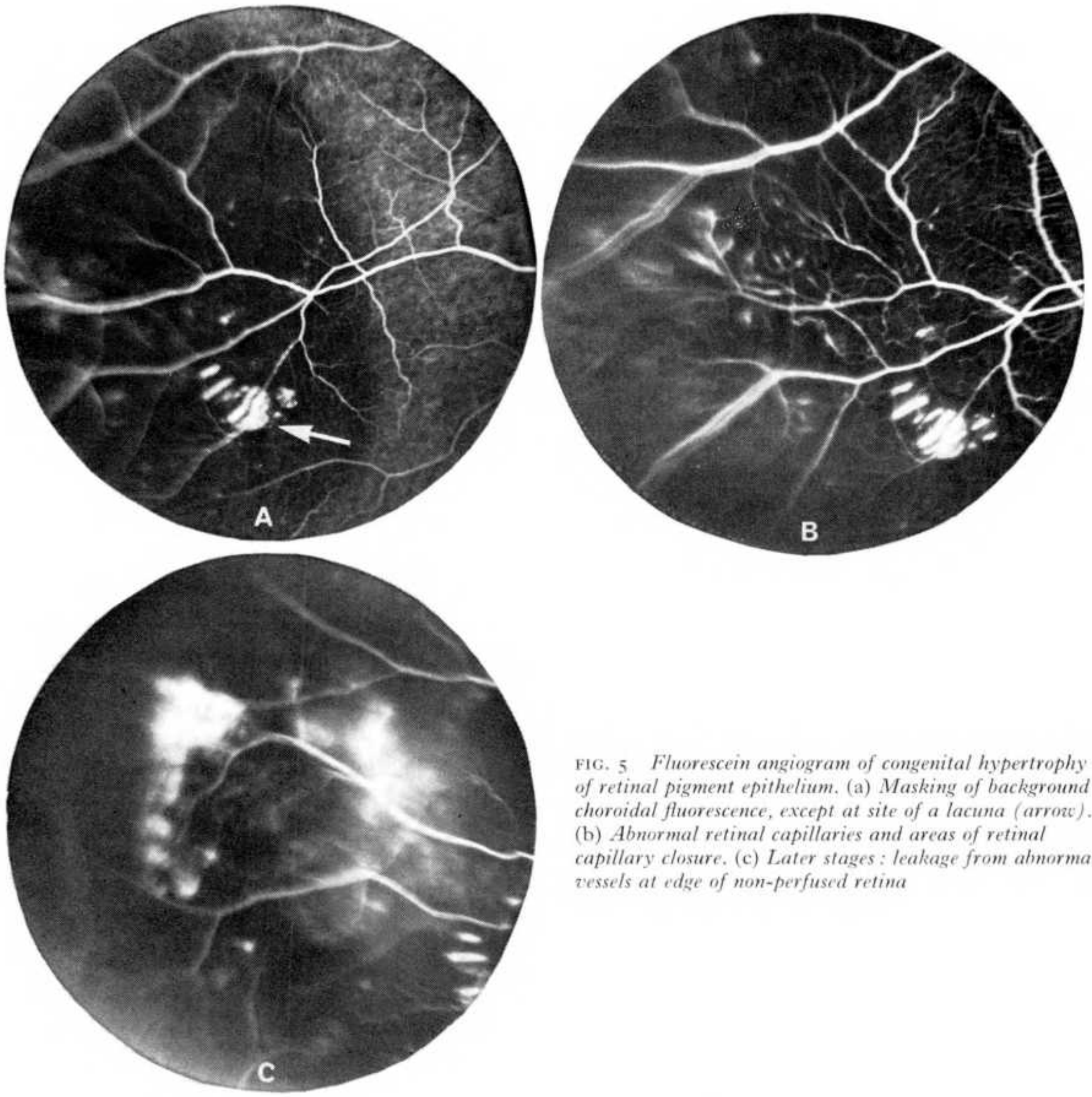

FIG. 5 *Fluorescein angiogram of congenital hypertrophy of retinal pigment epithelium.* (a) *Masking of background choroidal fluorescence, except at site of a lacuna (arrow).* (b) *Abnormal retinal capillaries and areas of retinal capillary closure.* (c) *Later stages: leakage from abnormal vessels at edge of non-perfused retina*

directly related to the state of the inner retina (Gerstein and Dantzker, 1969).

It has been argued that outer retinal atrophy would result in an increased oxygen concentration in the inner retina because of the combined effect of reduced metabolic requirements by the outer retina and closer apposition of the inner retina to the choroid (Noell, 1953; Gerstein and Dantzker, 1969). Such an increase in oxygen tension caused vasoconstriction of retinal arterioles and veins (Dollery, Hill, Mailer, and Sousa Ramalho, 1964), and this may account for obliteration of retinal vessels in the presence of outer retinal atrophy (Gerstein and Dantzker, 1969).

This does not completely explain the retinal vascular occlusion associated with outer retinal atrophy. Mature retinal vessels are known to be remarkably immune to high concentrations of oxygen and, moreover, retinal capillary obliteration has not been successfully produced in adult animals exposed to high concentrations of oxygen, although in these animals a high oxygen tension was maintained for only a few weeks (Ashton, 1966, 1976). However, obliteration of retinal arterioles due to gross thickening of their walls has been observed histopathologically in cases of retinal dystrophy (Ashton and Tripathi, 1976), and possibly a prolonged high oxygen concentration might cause arteriolar constriction with a reduced blood flow to more distal tissues producing significant ischaemia. This could certainly account for the retinal capillary closure and leakage overyling CHRPE, which are reminiscent of the changes in branch or central retinal vein occlusion—changes usually assumed to imply retinal ischaemia rather than a high oxygen tension.

Summary

The overlying retinal blood vessels were abnormal in five cases of congenital hypertrophy of the retinal pigment epithelium. This illustrated the well-recognized association between outer retinal degeneration and obliteration of the overlying retinal vasculature. The proposed pathophysiological mechanisms, however, seem inadequate to explain completely the morphological changes of the retinal blood vessels in the presence of atrophy of the outer retina.

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Retinal vascular changes in bull's eye maculopathy

AMRESH CHOPDAR
From the Fundus Clinic, Moorfields Eye Hospital, London

Chloroquine toxicity produces a typical macular degeneration commonly described as 'bull's eye' retinopathy (Hobbs, Sorsby, and Freedman, 1959; Kearns and Hollenhorst, 1966). Since its recognition, similar macular appearances have been described in various other conditions without ingestion of chloroquine (Krill and Deutman, 1972; Deutman, 1974; Weise and Yannuzzi, 1974). One such case is described in this paper and the possible nature of the aetiology is discussed.

Case report

A 51-year-old White woman was seen in the fundus clinic of Moorfields Eye Hospital. She had a history of slow progressive loss of central vision in the right eye during the previous 12 months, but had not found it difficult to adjust to the dim light. Her only son has also been examined and found to have no ocular disease. In the past she had taken fenfluramine to control obesity and at the time of presentation and for the previous four years was taking methaqualone.

OCULAR FINDINGS

The visual acuity was counting fingers in the right and 6/9 in the left eye. The external slit-lamp examination, including ocular motility, were normal. The fundi showed identical involvement at each macula. The central macular area looked a deeper red than normal and surrounding it a halo-like zone could be seen with many white, shiny, dot-like particles, giving the typical 'bull's eye' phenomenon usually seen in chloroquine retinopathy (Fig. 1). These white dots were found to be retinal pigment epithelial defects when examined with a fundus viewing contact lens. The circle of punctate epithelial defect was in turn encircled by a ring of grey retina through which the underlying choroidal vessels could be seen with little difficulty. The peripheral retina in the temporal part of the right eye showed sheathing of vessels with tortuosity and arterio-venous anastomosis. Peripheral to the area of anastomosis there was an abrupt end to the retinal circulation; this was evident from the change in colour between the two zones. The poorly perfused peripheral retina showed several areas of round atrophic patches with pigmented edges (Fig. 2). The left peripheral retina showed sheathing and tortuosity, but no arterio-venous anastomosis.

Fluorescein angiography showed a confluent punctate fluorescence surrounding a hypofluorescent macula. Around this complex was a faint fluorescent ring corresponding with the grey circle seen clinically (Fig. 3). The peripheral retina in the right eye showed arterio-venous anastomosis and demonstrated the abrupt cessation of the retinal circulation. The round atrophic patches showed transmission defects during the early stages and scleral staining during the later frames (Figs 4, 5).

RETINAL FUNCTION TESTS

The peripheral field showed some constriction in each eye. There was a central scotoma in the right eye but no such defect was seen in the left. The colour vision was normal in the left eye but could not be tested satisfactorily in the right owing to gross reduction of vision. The electroretinogram showed a scotopic B wave of 130 mV in the right and 200 mV in the left eye. The photopic response of the right eye was present with a good flicker response but the amplitude was significantly lower than in the left eye. Similarly the electro-oculogram was only 155 per cent in the right and 180 per cent in the left eye.

GENERAL PHYSICAL EXAMINATION

The patient was moderately obese with a blood pressure of 130/80 mmHg. The cardiovascular, respiratory, abdominal, and central nervous systems were all normal.

LABORATORY INVESTIGATIONS

The haematological examination showed haemoglobin 15 g/100 ml, packed cell volume 42 per cent, mean cell haemoglobin concentration 36 per cent, total white cell count 9000/mm^3, neutrophils 57 per cent, eosinophils 3 per cent, lymphocytes 33 per cent, monocytes 7 per cent, erythrocyte sedimentation rate 5 mm in 1 hour (Westergren), and no gross abnormality in the red blood cells. The biochemical estimation of total serum protein was 7·2 g/100 ml, albumin 4·2 g/100 ml, globulin 3·0 g/100 ml with a normal electrophoretic pattern. The immunoglobulin assay showed a slight increase of IgM at 325 IU/ml but normal values for IgG, IgA, and IgD. Serological tests for syphilis and Reiter's syndrome were negative.

Discussion

Maculopathy mimicking chloroquine toxicity in cases of cone dystrophy was described by Krill and

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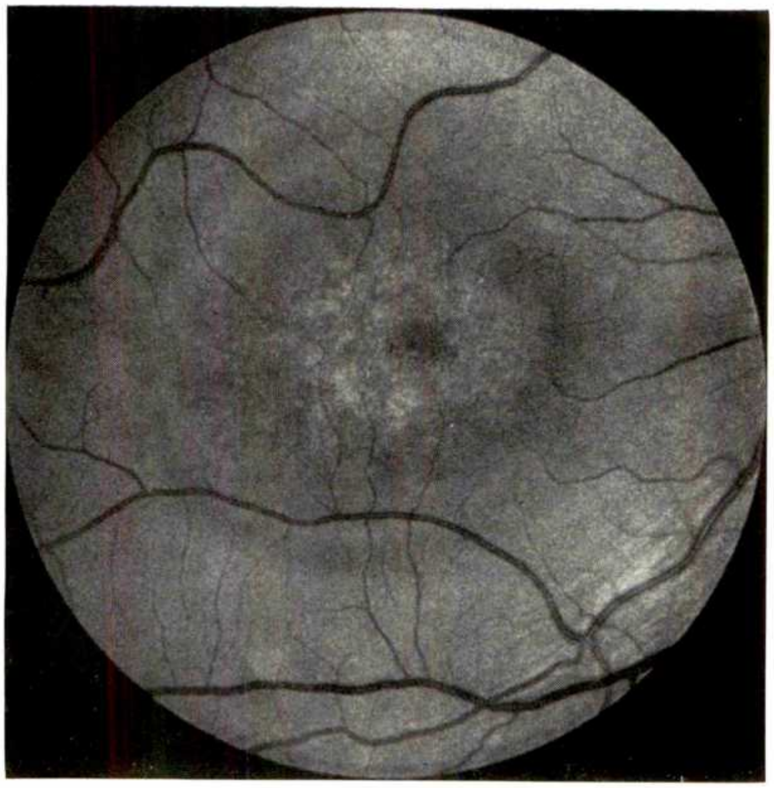

FIG. 1 *Red free photograph of right macula showing a darker fovea, surrounded by many white spots, lying within a ring of grey retina*

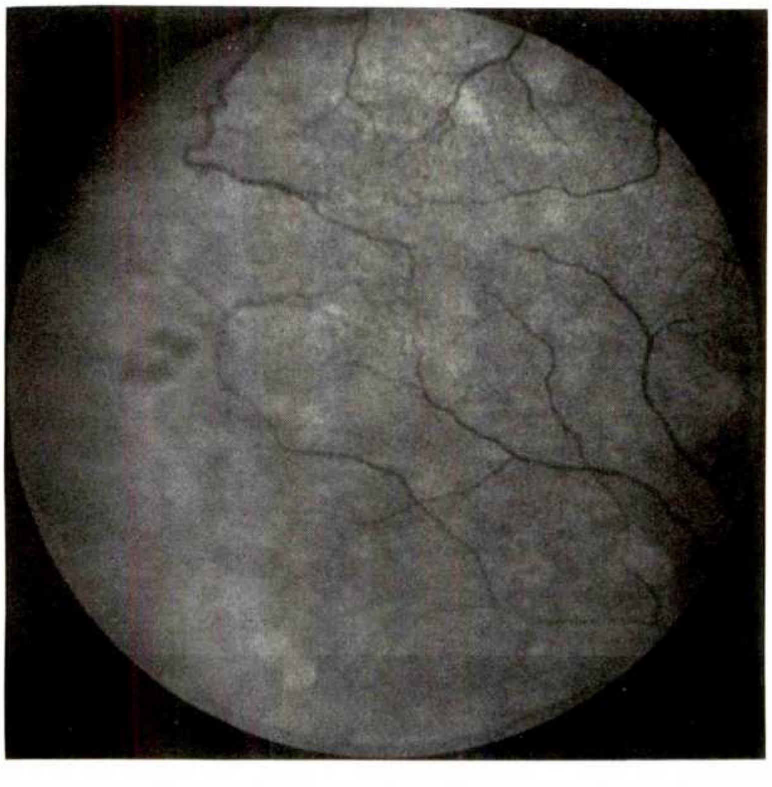

FIG. 2 *Red free photograph of right temporal periphery showing vascular abnormalities and poor peripheral retinal circulation*

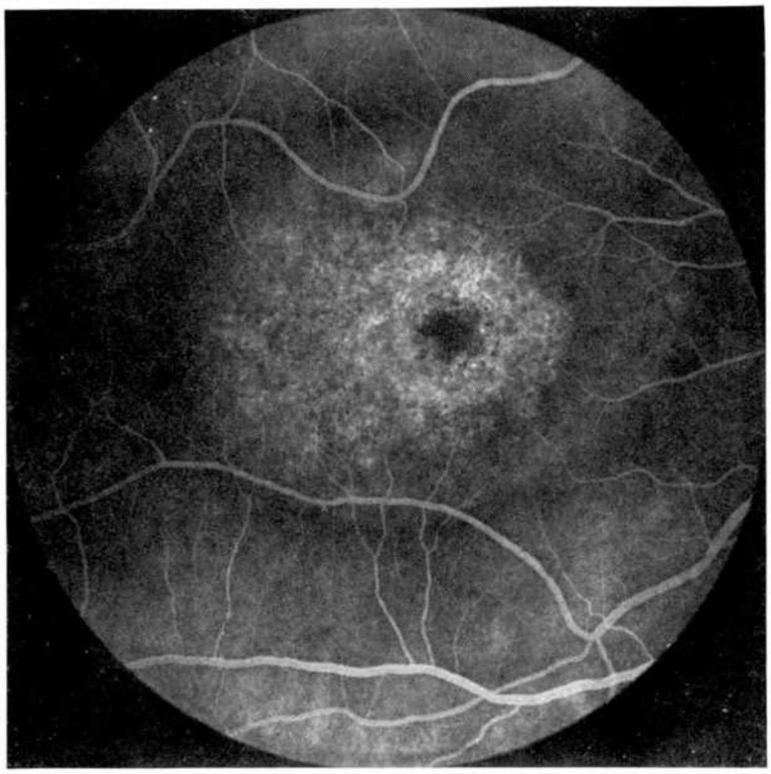

FIG 3 *Fluorescein angiography of right macula showing confluent punctate fluorescence surrounding a hypofluorescent fovea, similar to that of chloroquine toxicity*

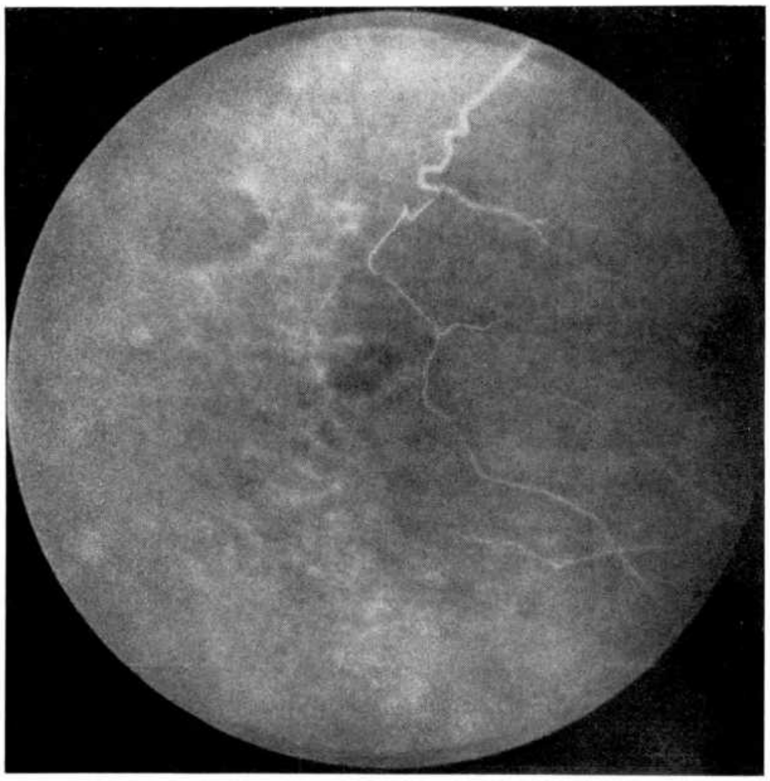

FIG. 4 *Fluorescein angiography of right temporal periphery showing arterio-venous anastomosis and poor retinal circulation peripheral to the anastomosis (slightly touched to obtain contrast)*

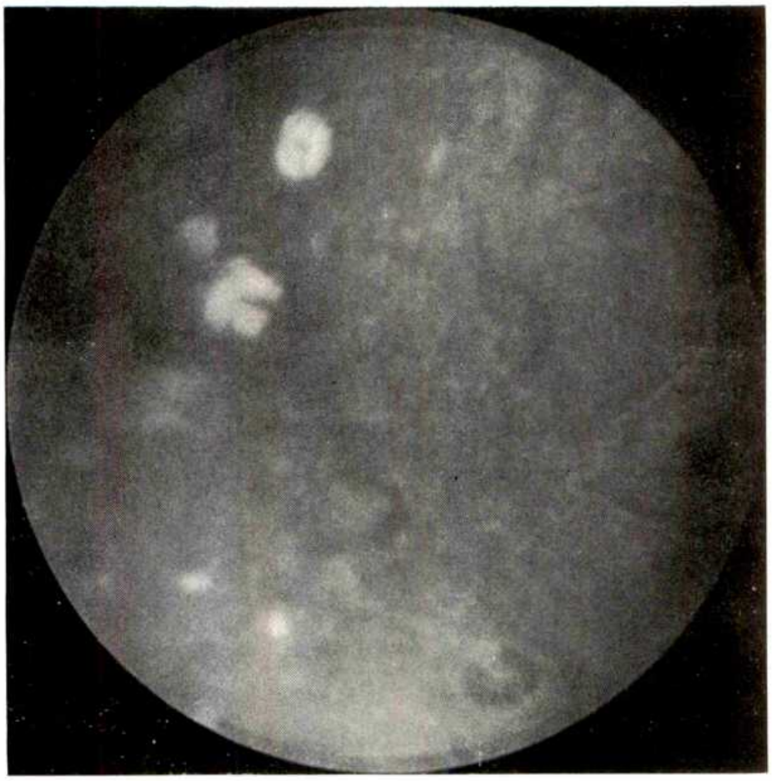

FIG 5 *Fluorescein angiography of the right temporal periphery 10 min after the injection of dye, showing scleral staining of the atrophic patches*

Deutman (1972). These patients suffered from severe loss of central and colour vision. Later, Deutman (1974) reported a case of autosomal dominant macular degeneration which he called benign concentric annular macular dystrophy which had similar fluorescein results but good visual acuity. Weise and Yannuzzi (1974) made a fluorescein angiographic study of ring-like transmission defects around the macular area in patients not suffering from chloroquine toxicity and obtained somewhat similar pictures in Stargardt's disease, pre-disciform macular degeneration, and resolved central serous retinopathy; on several occasions the diagnosis was thought to be progressive macular degeneration of unknown aetiology.

The case described here had signs resembling chloroquine toxicity, in addition to the peripheral retinal vascular changes not seen earlier. No instances of toxicity ascribed to methaqualone or fenfluramine have been found in the literature, and genetic evidence is inadequate as the only available relative (the son) is normal. The aetiology remains obscure.

Summary

A case of maculopathy mimicking chloroquine toxicity without exposure to the drug is described. The peripheral retina showed sheathing and arterio-venous anastomosis with poor perfusion of the retinal circulation.

I thank Professor D. W. Hill for permission to report this case and for his helpful criticism; Mrs Ann Marie Turk for the illustrations, and Mrs Joyce Preen for secretarial help.

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Ocular findings in a case of fucosidosis

MARJORY B. SNODGRASS
From the Stirling Royal Infirmary, Scotland

In fucosidosis an inborn error of metabolism causes a deficiency of α-L-fucosidase. The clinical picture was first identified by Durand, Borrone, and Della Cella (1966) and the biochemical abnormalities first described by Van Hoof and Hers (1968). Fourteen cases have so far been reported. The inheritance of the condition is autosomal recessive in type. In some cases relatives have been shown to be carriers of the defect with a level of α-L-fucosidase midway between normal and that found in the established disease.

Fucosidosis presents gross neurovisceral disorders and there are two clinical groups. In the first there is severe progressive cerebral degeneration with gradual muscle loss and spasticity leading to decerebrate rigidity and death in the first few years of life. In the second group the signs appear later and deterioration is slower. In addition to neurovisceral changes there may be gross skeletal abnormalities. Some cases in the second group have a generalized skin lesion which develops slowly and resembles the angiokeratoma corporis diffusum of Anderson-Fabry disease (Wallace, 1973), but it differs in that the characteristic glycolipid material is absent and also the α-galactosidase level in leucocytes and fibroblasts is normal.

The ocular findings in fucosidosis have not been described in detail. Gatti, Borrone, Trias, and Durand (1973) reported 'slight cloudiness of corneae' in some cases. Borrone, Gatti, Triad, and Durand (1974) reported 'strabismus' with 'papilloedema with congestion and tortuosity of retinal vessels' in one case and 'thin and tortuous vessels' in an affected sibling (Ng, Donnell, and Kock, 1973).

Case report

The case was the first to be recorded in the UK. Primrose (1972) reported the clinical details and MacPhie, Logan, and Primrose (1975) the diagnostic biochemical finding of absence of α-L-fucosidase. The patient, a 24-year-old Caucasian woman, was an only child. Her mother was dead and her father was unknown. Her maternal grandfather was himself the only surviving child of a first-cousin marriage. She is now severely mentally retarded. She sees well enough to recognize people, hears normally, and is able to say an occasional word. Neurological degeneration is progressive with resulting flexion contractures of legs and arms. Her features are coarse, resembling gargoylism (Fig. 1), and her skull is large (circumference 56 cm, length 18·5 cm, breadth 15 cm, cephalic index 0·81). Her tongue is also large and coarsely fissured, her neck is short, and she has pronounced dorsal scoliosis. Her hands and fingers are long and straight. Positive *x*-ray findings include prognathism, deformities of ribs, scoliosis with partial fusion of lower thoracic vertebrae, and gibbous deformity of lumbar vertebrae. In the wrists scaphoid, trapezium, and trapezoid bones are absent (Fig. 2). The most striking feature is a generalized skin condition (Fig. 3) consisting of red to dark red macules and papules, especially on the breasts, thighs, and pelvic area. Blood can be expressed from some but not others, which appear papillomatous—especially in flexural areas. Histologically they are reported to be 'simple lymphangiomas with a marked angiomatous element'.

The eyelids have an antimongoloid slant. The distance between the inner canthi is 35 mm and between the outer 102 mm. There is an alternating concomitant divergent strabismus (−15° to −20°). With eyes fixing centrally in alternation, the interpupillary distance is 73 to 74 mm. There are small red macules and spider naevi on the lids and brow which empty on pressure.

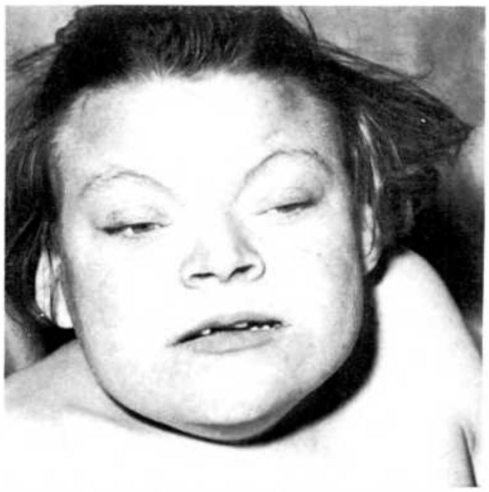

FIG. 1 *Coarse features resembling gargoylism*

Address for reprints: Dr M. Snodgrass, Stirling Royal Infirmary, Stirling, Scotland

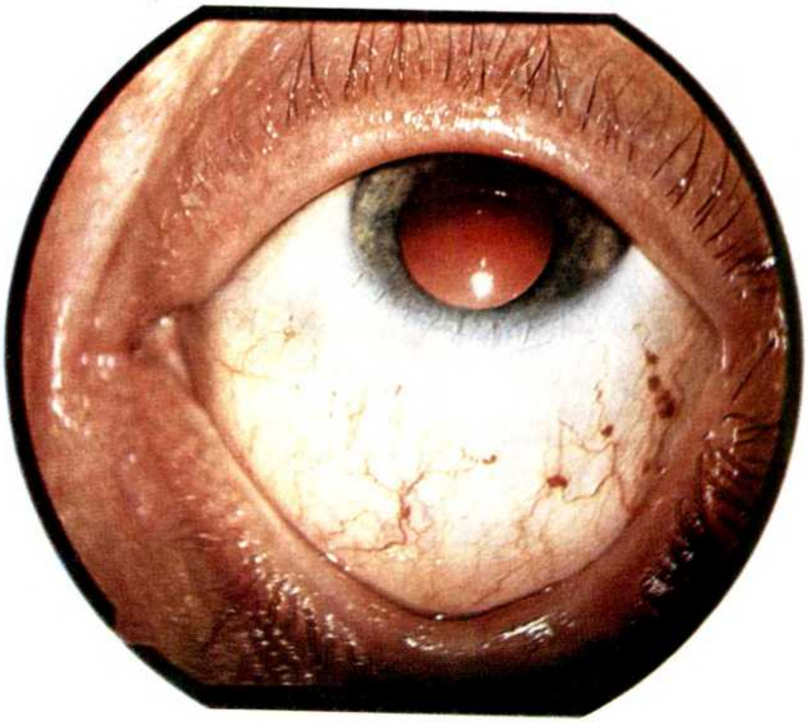

FIG. 4 *Dilated, tortuous conjunctival vessels, some with saccular dilatations*

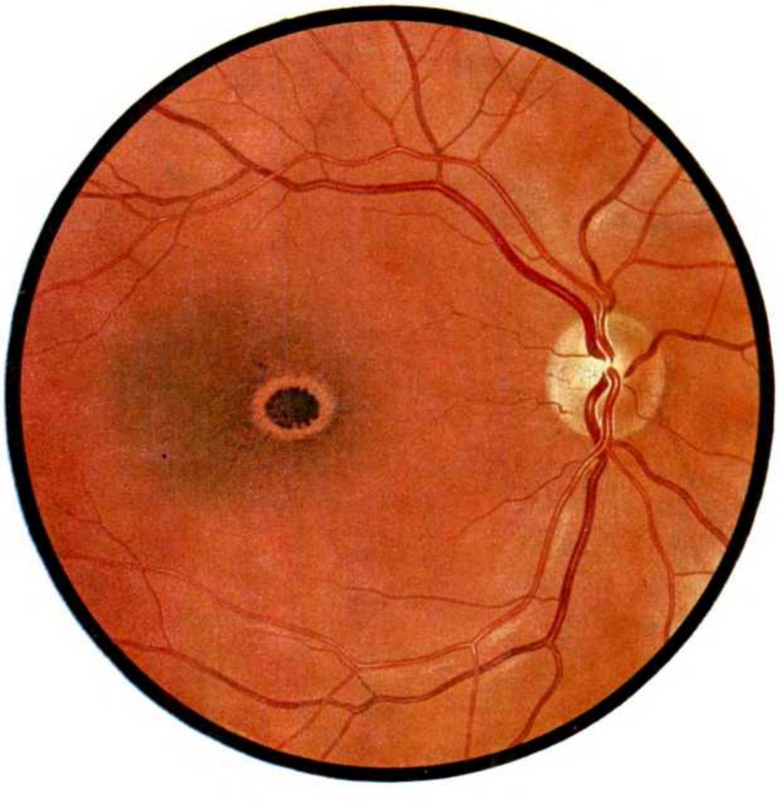

FIG. 5 *Fundus of left eye (painted from description given by author)*

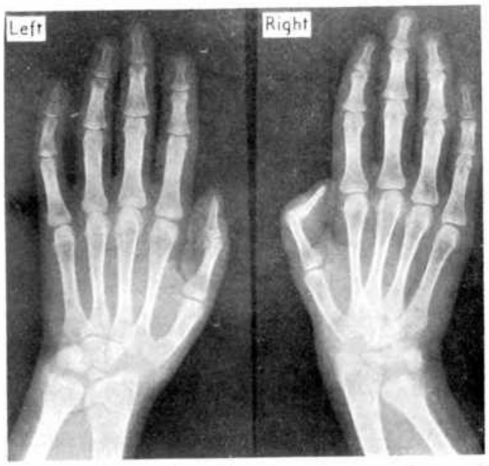

FIG. 2 *X-ray films of hands and wrists: absence of scaphoid, trapezium, and trapezoid bones*

Blepharospasm is frequent. Both bulbar and, to a lesser extent, palpebral conjunctivae, have dilated tortuous vessels, some with saccular dilatations (Fig. 4). There is a moderate hypermetropic astigmatism with the rule. The corneae are oval transversely (estimated vertical diameter 10 mm, horizontal 12 mm) due to some scleralization at the limbus above. The anterior chambers are of normal depth and the corneae and lenses are clear. The fundi show macular changes resembling bull's eye retinopathy. The foveal area has fine brown pigmentation and is ringed by a zone of hypopigmentation. The rest of the macular area has fine brownish, slatey-blue pigmentary change with occasional clumps of dark brown pigmentation. The discs and vessels are healthy and there is no undue tortuosity of the vessels. In the equatorial region in the left eye near the inferior temporal vessels are two small brown pigmented spots surrounded by an areola of hypopigmentation (Fig. 5).

The patient's maternal grandfather, the only relative able to be examined, is physically and mentally normal and his fundi are healthy. His α-L-fucosidase level is about half of normal.

Discussion

Unfortunately, because of the patient's almost complete inability to co-operate and her blepharospasm, special examinations could not be performed. The general appearance and x-ray changes in ribs, spine, and wrists are similar to those found in gargoylism. However, she has no other clinical features or diagnostic enzymatic deficiencies to support a diagnosis of mucopolysaccharidosis.

The widespread maculo-papular rash and the saccular dilatations in the conjunctival vessels resemble those described by Velzeboer and de Groot (1971) in Anderson-Fabry disease. This diagnosis can be excluded by the absence of the characteristic histology and the presence of a normal α-galactosidase level. The fundal changes of bull's eye maculopathy resemble those first

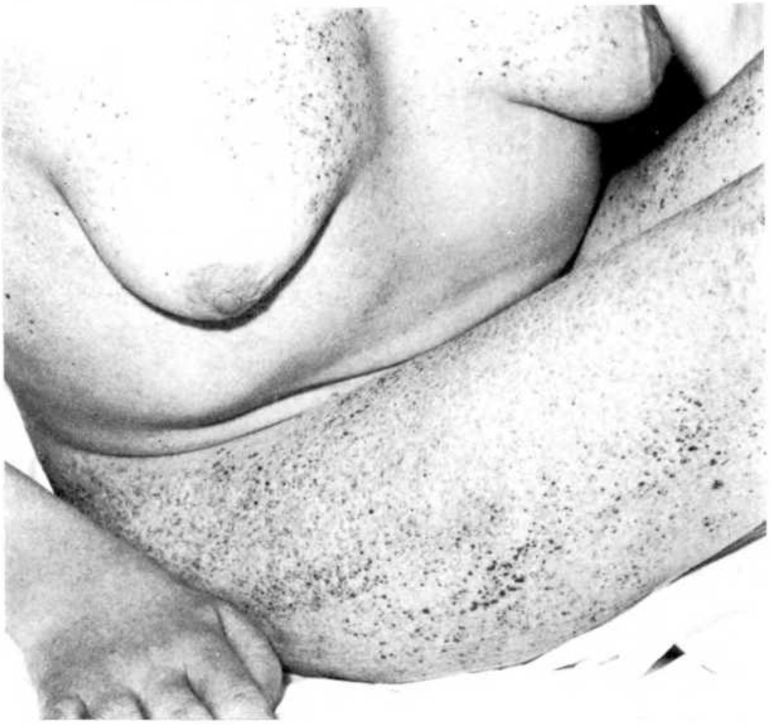

FIG. 3 *Generalized maculo-papular rash*

described by Hobbs, Sorsby, and Freedman (1959) in cases of chloroquine poisoning. Recently a similar clinical picture has been noted by Weise and Vannuzzi (1974) in nine patients in the absence of chloroquine therapy. This maculopathy has also been reported in children in a hereditary form by Deutman (1974). After extensive investigations he showed it to be due to degeneration of cones. Neither of these two groups of bull's eye maculopathy shows any clinical features of fucosidosis, but could there be a relative deficiency of the enzyme as a predisposing factor?

Summary

The ocular findings in a case of fucosidosis are described and the differential diagnosis is discussed. It is suggested that the level of α-L-fucosidase should be estimated in cases of bull's eye retinopathy.

I thank Dr J. Dudgeon, Department of Ophthalmology, University of Glasgow, for his helpful advice, and Mr G. Donald, Director of Medical Illustration, Glasgow Western Infirmary, for his fundus painting. The Carnegie Trust is thanked for assistance in the reproduction of the colour illustrations.

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Annular choroidal sclerosis

A. CHOPDAR
Fundus Clinic, Moorfields Eye Hospital, High Holborn, London

Annular choroidal sclerosis is a rare kind of fundus disease. It was first described by Knapp (1907) but later Schocket and Ballin (1970) added two more cases to the literature.

Material and methods

CASE REPORT

A 29-year-old White man was seen in the fundus clinic of Moorfields Eye Hospital in September 1974. He had a history of gradual deterioration of vision in both eyes for the past five months. He had been seen elsewhere earlier that year when visual deterioration first became noticeable in the right eye, with a diagnosis of central serous retinopathy, and had received a course of systemic corticosteroids. One month later symptoms began in the left eye, while still on systemic corticosteroid treatment, and he was referred to the fundus clinic. He gave no history of any previous ocular or systemic illnesses. There was no family history of similar disease or of consanguinity.

OCULAR EXAMINATION

The visual acuity was 6/18 in each eye. External examination—including slit-lamp biomicroscopy, pupillary responses, and extraocular movements—was normal. The fundi showed bilateral symmetrical annular bands of depigmentation beginning at the upper part of the optic disc, passing along the course of the upper temporal vessels; and circling round an oedematous macula. This circle of depigmentation was somewhat incomplete inferiorly. There were a few pigment clumps on the surface of the retina along the band of depigmentation, but no evidence of narrowing of the retinal blood vessels or optic atrophy.

The fluorescein angiogram showed early background choroidal fluorescence through the defective retinal pigment epithelium, surrounding a hypofluorescent macula, in a horse-shoe manner. The lower incomplete part showed spotty windowing. The late frames of the angiogram showed leakage into the macula and scleral staining corresponding to the depigmented band (Fig. 1).

Eighteen months after the onset of symptoms his visual acuity and visual fields had remained unchanged. The fluorescein angiogram showed there was very little leakage into the macula, and no further advance of the choroidal sclerosis.

RETINAL FUNCTION TESTS

Perimetry revealed an incomplete ring scotoma between the 10° and 20° isopters around the point of fixation in each eye which matched very closely to the band of depigmentation seen clinically (Fig. 2). The colour vision was normal. The dark adaptation curve showed a rise in the final threshold by 1½ log units. The electro-oculogram was flat, while the electroretinogram was reported to be normal.

LABORATORY EXAMINATIONS

The haematological examination showed haemoglobin 15·4 g/100 ml, total white cell count 9000 mm^3, neutrophils 57 per cent, lymphocytes 34 per cent, eosinophils 4 per cent, monocytes 5 per cent, packed cell volume 44 per cent, mean cell haemoglobin concentration 34 per cent, and erythrocyte sedimentation rate 4 mm in 1 hour. Serological tests for syphilis and Reiter's syndrome were negative.

PEDIGREE

The seven-year-old daughter of this patient had a visual acuity of 6/6 in each eye. Her fundi showed gross retinal pigment epithelial disturbance and a faint arc of depigmentation extending both upwards and downwards adjacent to the temporal border of the optic disc. Fluorescein angiography revealed patchy choroidal filling and windowing owing to defective retinal pigment epithelium. The depigmented arc at the temporal border of the optic disc gradually took on a somewhat oval-ring shape, and showed some loss of choriocapillaris. Both maculae were normal (Fig. 3). No other member of the family showed any such clinical signs (Fig. 4).

Discussion

The case described here has many findings similar to those reported by the previous authors as circinate choroidal sclerosis (Knapp, 1907; Schockett and Ballin, 1970). Zimmerman and Fitzgerald (1975) described a case of 'peculiar degenerative choroidal sclerosis' affecting both

Address for reprints: A. Chopdar, FRCS, Fundus Clinic, Moorfields Eye Hospital, High Holborn, London WC1V 7AN

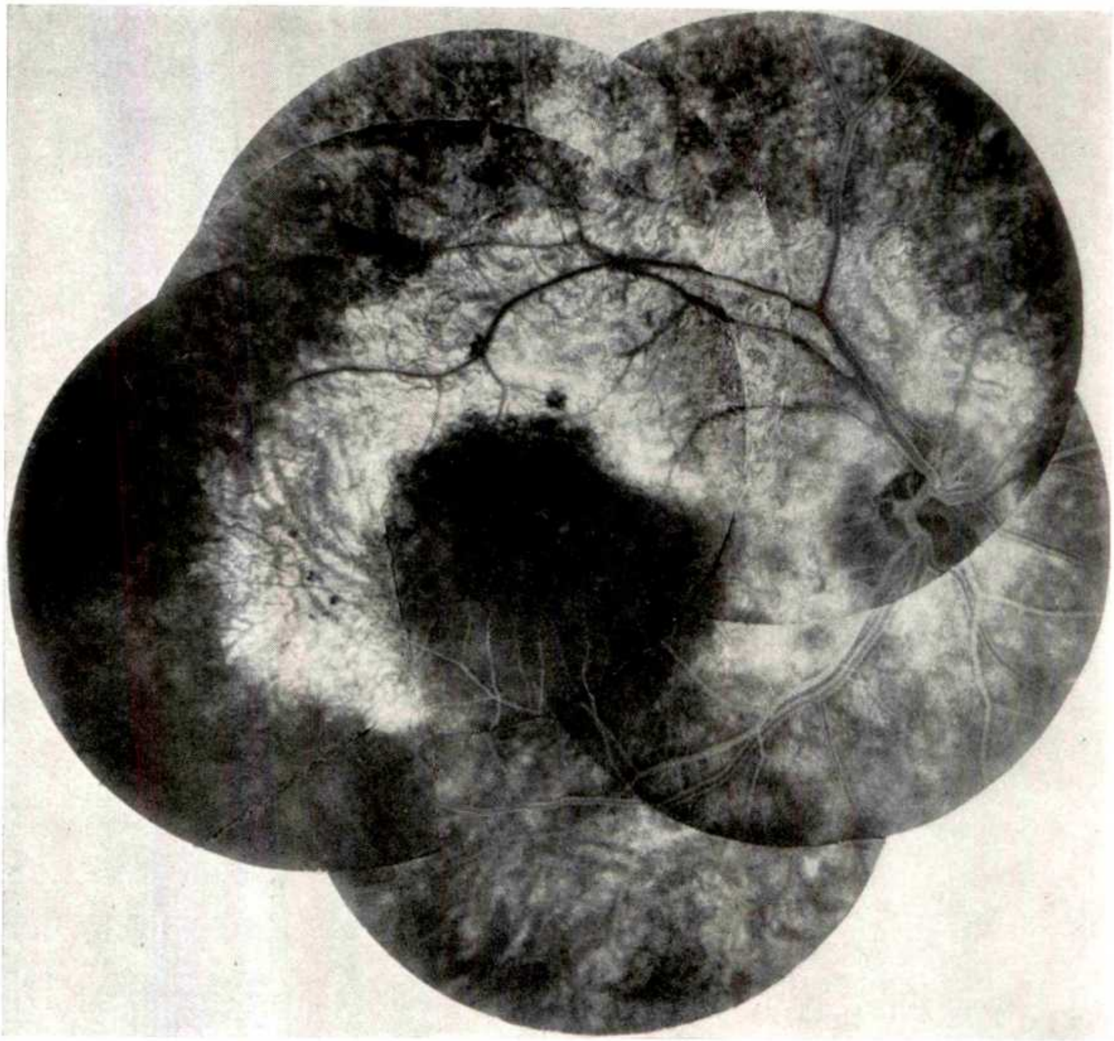

FIG. 1 (a) *Composite fundus photograph of right eye, from various stages of fluorescein angiography, showing annular choroidal sclerosis*

eyes in a 60-year-old man, with many features similar to circinate choroidal sclerosis. The term 'annular' has been chosen to avoid confusion with the well-established circinate retinopathy seen in various fundus disorders.

Annular choroidal sclerosis, although rare, is a definite entity. Careful analysis of all reported cases showed bilateral occurrence in both sexes at all ages. The visual acuity may also be reduced depending upon the amount of damage to the macula. From this fluorescein study it was apparent that the initial lesion lay in the choriocapillaris, leading to degeneration and atrophy of retinal pigment epithelium which progressed in an annular pattern from the optic disc round the macula. Macular oedema during the active phase of the disease was probably due to damaged choriocapillaris and altered metabolism of the retinal pigment epithelium. Later the activity subsided and the macular oedema resolved, leaving an annular band of choroidal sclerosis around the macula. The flat electro-oculogram suggested widespread damage of the outer layer of the retina, probably secondary to the impaired choroidal circulation.

In this family the genetic evidence is inadequate, although the seven-year-old daughter did show some of the signs of the disease both clinically and angiographically. It has not been possible to com-

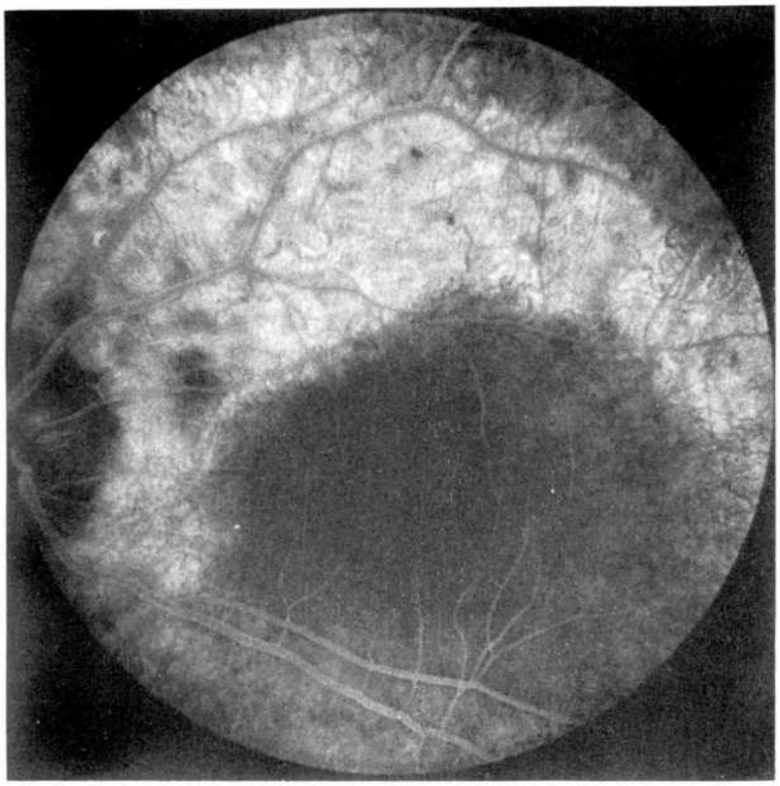

FIG. 1 (b) *Fluorescein angiographic appearance of left fundus,* 10 *min after injection of dye showing an annular pattern of choroidal sclerosis, similar to that of right eye*

plete all the desired investigations on this very young girl because of lack of co-operation, and it will need many years of follow-up to see if the full form of the disease will develop.

Defective electrodiagnostic results and abnormal dark adaptation would arouse suspicion of tapetoretinal degeneration such as retinitis pigmentosa and choroideremia. Central choroidal sclerosis and

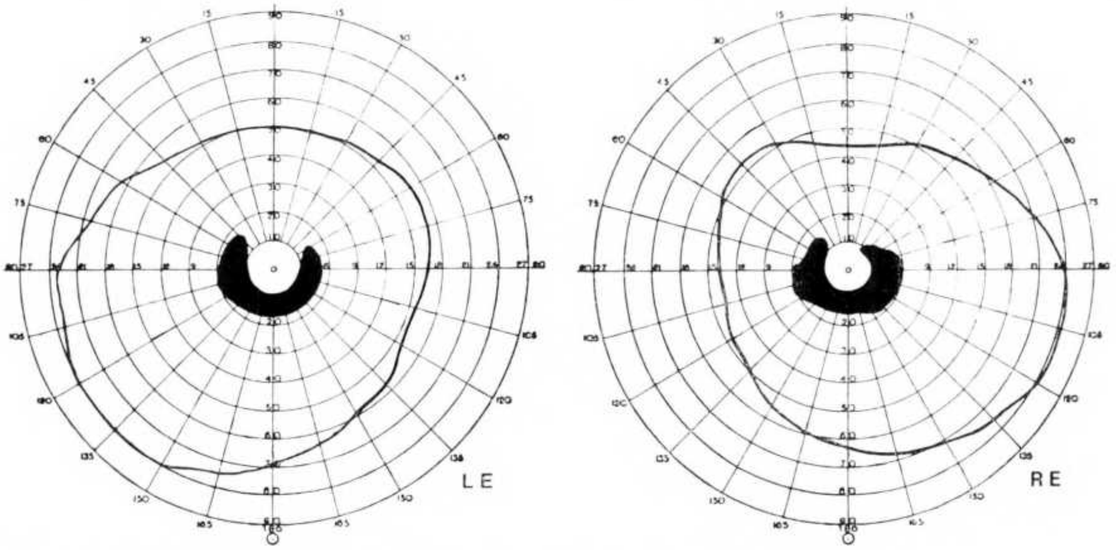

FIG. 2 *Visual fields showing ring scotomas matching choroidal sclerosis seen in Fig.* 1

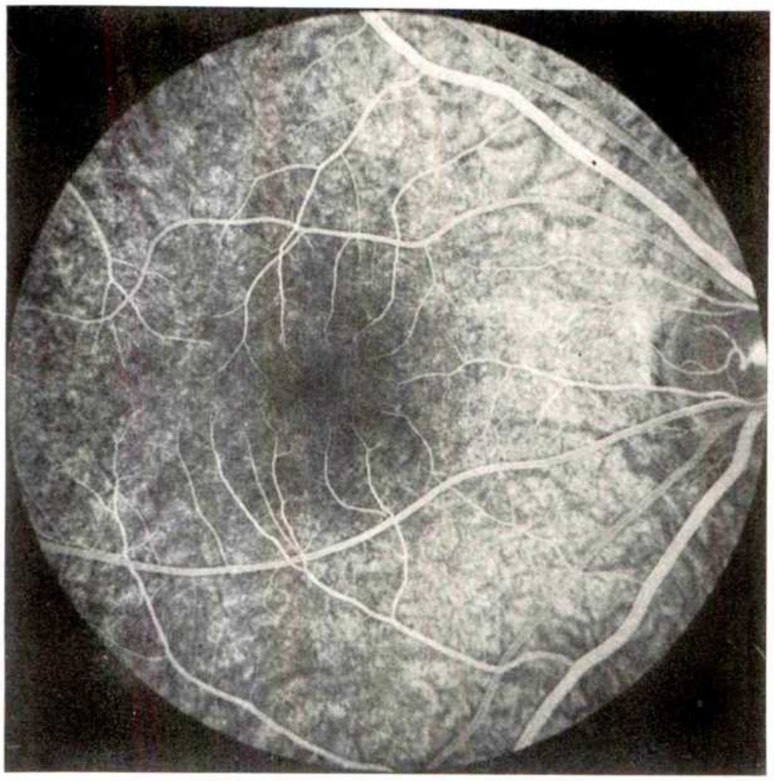

FIG. 3 (a) *Fluorescein angiographic appearance of right fundus of daughter, during venous phase, showing patchy background choroidal fluorescence due to defective retinal pigment epithelium in a somewhat ring-shaped manner, especially temporal to optic disc*

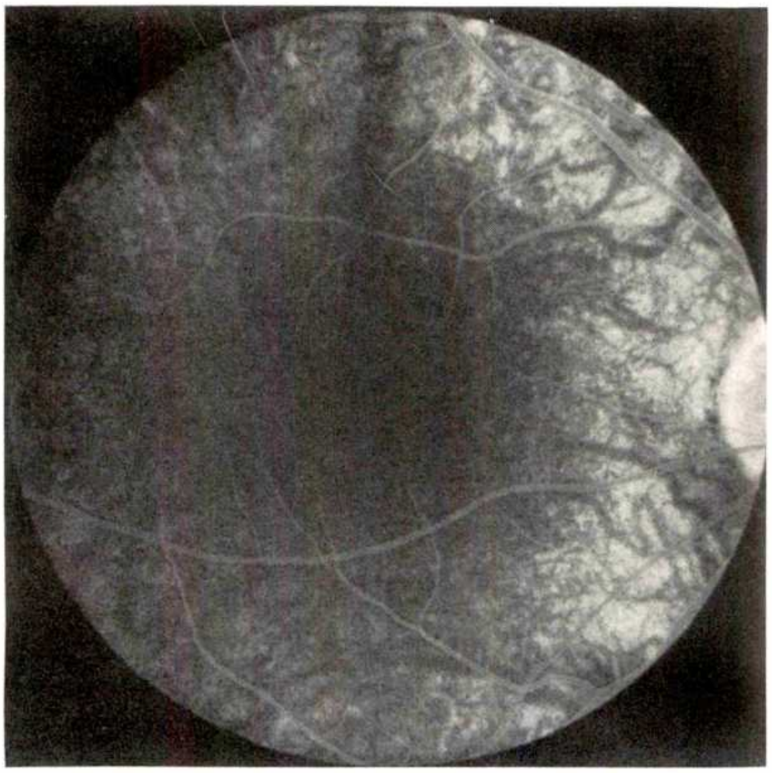

FIG. 3 (b) *Same eye as* (a) 10 *min after injection of dye, showing more definite annular pattern*

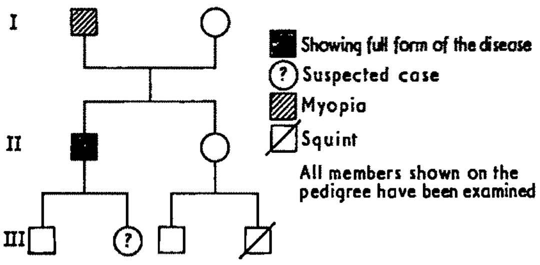
I
II
III
Showing full form of the disease
?
Suspected case
Myopia
Squint
All members shown on the pedigree have been examined

FIG. 4 *The pedigree*

geographical choroiditis may at times be confused with annular choroidal sclerosis because of macular oedema, but in all these cases the visual acuity is severely affected and atrophic changes start at the macula. Rarely myopia and albinism might be suspected because of the sparseness of the retinal pigment epithelium.

Summary

This is a case description of a rare fundus condition known as annular choroidal sclerosis. No more than four previous cases have so far been reported. In this article consideration is given to the pathogenesis of the disease and a possible familial link.

I thank Professor David W. Hill for his helpful criticism and permission to report this case under his care. I also thank Mrs Ann Marie Turk for the illustrations and Mrs Joyce Preen for her secretarial help.

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Distribution of myopia in aphakic retinal detachments

MONTAGUE RUBEN AND PUSHPA RAJPUROHIT
From the Contact Lens and Prosthetics Department, Moorfields Eye Hospital, London

The aetiology of retinal detachment after lens extraction requires analysis to determine common factors. According to Treister (1972) an increased incidence is due to the use of chymotrypsin. Shapland (1934) quotes an overall incidence of 2·2 per cent using the extracapsular technique. He thought it to be higher in myopic aphakia but he gave no figures. Hyams, Bialik, and Neumann (1975) give an incidence of 6·7 per cent for myopia above -6·00. The factors that may be considered statistically are age, sex, surgical technique, type of anaesthesia, and precataract refractive error.

Details of surgical technique are difficult to analyse, but the essential procedures may be grouped easily into extra- and intracapsular removal of the lens, cryoextraction, and use of enzyme. Complications such as vitreous loss may also be clearly indicated. Results may be analysed by using corrected acuity as the yardstick, though the incidence of poor acuity after extraction is likely to be high in degenerative myopia, complicated cataracts, traumatic cataracts, and infantile cataracts. The results analysed in this paper exclude infantile cataracts, in which the incidence of detachment is high (Shapland, 1961) and the acuity poor (Ruben, 1969).

By analysing the results of almost 1000 cataract extractions for the incidence of detachment and for visual acuity and a random group of them for refractive error power corrections we hoped to show the role of myopia in the incidence of aphakic retinal detachment. In order to obtain these results a schematic aphakic eye was introduced so that the precataract refractive state could be easily calculated.

Patients and methods

The operation records and in- and outpatient notes were studied of all patients operated on for cataract by the corneo-scleral section lens extraction procedure at the High Holborn Branch of Moorfields Eye Hospital in the three years 1967–9. All aspirations and washouts were excluded. The following information on each patient was noted: age at time of operation; sex; details of operation (general anaesthetic, extra- or intracapsular or cryoextraction, forceps, type of section, vitreous loss); postoperative data; best acuity with spectacles; preoperative refractive state (when recorded); detachment of retina in the postoperative aphakic state or in the phakic state at time of operation; site of retinal tears; acuity after retinal surgery; referral of patients for fitting with contact lens.

SCHEMATIC APHAKIC EYE

A schematic aphakic eye was used to relate the postoperative to the precataract refractive state.

Given an average phakic power of +60·00 and an average keratometry of 7·80 (RI = 1·37), the average spectacle power at a back vertex distance (BVD) of 15 mm = +13·50. Thus for each refraction postoperatively the equivalent sphere was found and the ocular refraction calculated (BVD = 15 mm). The difference between the two gives the preoperative refractive state. It would be unwise for these figures to assume a tolerance greater than ±1·00 and therefore the grouping of the results will be in 5 dioptres.

The following is an example of the calculation. Spectacle refraction = +14·00/+2·00 × 180 (BVD 15); equivalent sphere refraction = +15·00; schematic spectacle refraction = +13·50; therefore the preoperative refractive state = +1·50 hypermetropia (no effective power correction for ocular refraction unless over 5 dioptres).

Results

The results are given, first, as general data and, secondly, those that specifically refer to aphakic detachment of the retina.

GENERAL DATA

The total number of operations was 944 (Table I). For each year the numbers were 332, 350, and 260 respectively. Of the total number 896 were unilateral operations and within the period 48 patients had the other cataract removed. Thus 944 cataract operations represent 896 patients. Their average age was 65 and 448 were men and 448 were women.

During the period 1967–69 there was a rapid increase both in the use of general anaesthesia and of the cryo probe for lens extraction (Table II).

Address for reprints: M. Ruben, FRCS, Department of Contact Lens and Prosthetics, Moorfields Eye Hospital, High Holborn, London WC1V 7AN

Table I *Numbers of cataract operations, patients, and aphakic detachments*

Year	*No. of patients*	*No. of operations*	*No. (per cent) of detachments*
1967	304	332	18 (5·4)
1968	344	350	19 (5·4)
1969	248	262	17 (6·4)
Total	896	944*	54 (5·7)

*Unilateral=896 (95 per cent); bilateral=48 (5 per cent)

Table II *Use of general anaesthesia and cryoextraction for lens extraction in each of the three years* 1967–9

Year	*No. of operations*	*General anaesthesia No. (per cent)*	*Cryoextraction No. (per cent)*
1967	332	53 (12)	34 (10)
1968	350	287 (82)	191 (54)
1969	262	220 (84)	262 (100)
Total	944*	560	487

*Extracapsular extraction 53 (5·6 per cent); intracapsular extraction 891 (94·3 per cent). Inferior section used in 8 glaucoma eyes

Table III *Best postoperative visual acuity in* 944 *cases of lens extraction*

Acuity	*No. (per cent) of cases*
HM to CF	88 (9·6)
6/60–6/36	110 (11·9)
6/24–6/18	210 (22·9)
6/12–6/9	340 (37·0)
6/6–6/5	170 (18·6)
Not known*	26 (2·1)
Total	944 (100)

*Including blind eyes
HM=hand movements; CF=counting fingers

These years are therefore relevant to any discussion on the aetiology of retinal detachment in aphakia. Only eight cases had an inferior section and this number will not substantially affect the percentage incidence in the remaining 936 eyes.

The best postoperative spectacle correction findings are based on figures for only 918 eyes (Table III). These results will be discussed in relation to the phakic equivalent refractive state subsequently. Cases are grouped according to the visual acuities recorded in their notes by medical and sight-testing optician staff. When complications prevented measurement of acuity or none was given blindness could not be assumed. But it must be assumed that many of the 26 cases in which acuity was not known or unrecorded were, in fact, blind eyes. For the purposes of useful vision a corrected acuity better than 6/24 is a 'watershed', and 77 per cent fall within this category.

In 46 patients refractions done before operation revealed myopia between –10·00 and –20·00 (Table IV), and this will be commented on in relation to the estimated number of similar myopes for the whole group (Table V) and the figures quoted in Tables VI to VIII, which analyse the groupings of myopia in aphakia with detachment of retina.

Analysis of the 117 randomly selected refractions, using the schematic aphakic eye and its spectacle correction of +13·50, showed that 78·7 per cent were in the refractive group –4·00 to +4·00. This method can only approximate the precataract refraction state since the schematic eye calculations assume constants for BVD and refractive index (RI) and tolerances of refraction subjective testing, which are not known. For the purposes of this analysis 19·5 per cent were myopic over –5·00 and 7·70 per cent myopic over –10·00 in the precataract state.

The total number of retinal detachments occurring in the postoperative phase was 54 or 5·7 per cent of the total eyes operated on and the yearly analysis was 5·4, 5·4, and 6·4 (Table I). In some

Table IV *Patients with high preoperative myopia between* –10·00 *and* –20·00

Year	*No.*
1967	15
1968	17
1969	14
Total	46

Table V *Phakic equivalent refractive state in* 117 *randomly selected eyes with extrapolation for* 944 *eyes*

Refraction (117 eyes)		*No. (per cent) of cases*	*Extra-polation (944 eyes)*
Phakic equivalent	*Aphakic*		
–10·00 to –20·00	+3·50 to –6·50	9 (7·7)	69
–5·00 to –9·00	+4·50 to +8·50	15 (12·8)	119
–4·00 to 00	+9·50 to +13·50	78 (66·6)	640
+1·00 to +4·00	+14·50 to +17·50	14 (12·1)	108
Over +5·00	Over +18·50	1 (1·0)	8
Total		117 (100)	944

instances the detachment was bilateral. Thus there were 43 patients with 54 detachments, the incidence of bilateral detachment being almost 20 per cent of the detachment group. The sex distribution was men 65 per cent, women 35 per cent (Table VI). A male predominance was also noted by Shapland (1934). The average age (59) of the patients with aphakic detachments was lower than that of the whole group. This high incidence of bilaterality has also been noted by Kanski (personal communication).

In the detachment group 33 had known refractive powers. Of those aphakic patients in this study who had retinal detachments and whose refractions were known, no fewer than 16 out of 33 (50 per cent) had a refractive error of more than −10 dioptres (Table VIII). The distribution of refractive errors in the whole group of 944 eyes can be deduced by reference to a study of the data in a sample of 117 eyes in which the refractions were known (Table V).

It is possible to calculate from these data the incidence of retinal detachment in myopes of −10 dioptres or more. It is known that 50 per cent of all patients with detachments had refractive errors of −10 dioptres or more. This would give an expected figure in the whole sample of 944 of 27 eyes (50 per cent of the detachments) out of 69 eyes (the calculated number of eyes in the whole sample of aphakics with refraction of −10 dioptres or more). This gives an incidence of retinal detachment in aphakia, in which the original refraction was −10 dioptres or more, of 27 out of 69, almost 40 per cent. The expected incidence in the other refractive groups can be similarly calculated (Table VIII).

Table VI *Data on 43 patients (54 eyes) with aphakic retinal detachments (one traumatic detachment excluded)*

Sex	
Male	28 (65 per cent)
Female	15 (35 per cent)
Age (years)	
Average	59
Range	30–86
Detachment	
Unilateral	43 (80 per cent)
Bilateral	11 (20 per cent)

Table VII *Incidence of myopia in 54 eyes with aphakic retinal detachments*

Preoperative refraction	*No. of cases*		*Percentage (of 33 cases)*		
Emmetropia	8		24	42	24
0 to −4·00	6		18		76
−5·00 to −9·00	3		8	58	
−10·00 to −20·00	16	33	50		
Not known	21				
Total	54				

Table VIII *Probability of aphakic retinal detachments according to refractive error*

Refraction	*Incidence (per cent)*
In refractive groups	
0 to −4·00	3·5
−5·00 to −9·00	4·2
−10·00 to −20·00	40·0

Table IX *Operation data in 54 cases of aphakic detachment*

Data	*No. (per cent) of cases*
Intracapsular	52 (96)
Extracapsular	2 (4)
Cryo probe	32 (59)
Forceps	8 (15)
Chymotrypsin	19 (35)
Vitreous loss	6 (11)

Aetiological factors apart from myopia require analysis of the operation details (Table IX) and will be dealt with in discussion. But it is significant that for the years 1967, 1968, and 1969 (Table I) the incidence of detachment does not vary more than one per cent although the change from forceps to cryo probe extractions was more than threefold. The intra- extra-capsular extraction ratio and use of the cryo probe is not very different from that shown in Table II for the whole series and therefore not significant. Vitreous loss in the detachment group is significant (11 per cent) since the figures for the whole series were less than 1 per cent.

The period for analysis began in 1967 from the date of first operation and the case notes were studied up to the time of the survey (December 1975). We could therefore plot the time factor in the incidence of detachment (Table X). In 33 cases where information was clearly obtained two-thirds occurred in the first postoperative year and nearly one-third in the second.

While we did not originally intend to obtain information about the site of the retinal break this was clearly indicated in 36 eyes and the results are given (Table XI). Half of the eyes had a com-

Table X *Time of onset of retinal detachment after cataract extraction*

Time (months)	*No. of cases*	*First year*	*Second year*	*Third year or more*
1	6	21		
4	7			
8	6			
12	2			
24	10		10	
>24	2			2

Table XI *Site of break in retina in* 36 *eyes*

Site	*No. of cases*	
Temporal	6	
Upper		1
Lower		5
Nasal	12	
Upper		2
Lower		10
Complete	18	
Total	36	

plete detachment. But of the remaining 18, six showed temporal and 12 nasal retinal breaks. One was upper temporal, five lower temporal, 10 lower nasal, and two upper nasal—a pronounced preponderance on the lower retina and nasal side. There were insufficient data to relate this to vitreous wound inclusion and secondary retraction of vitreous.

Comparison of the visual acuities after retinal surgery (Table XII) with those for aphakia (Table III) shows a substantial loss in central acuity and almost fourfold incidence of blindness (less than 6/60).

Discussion

The use of the cryo probe and general anaesthesia for lens extraction increased almost fivefold in the period 1967–68, yet the incidence of detachment remained essentially the same. According to Treister (1972) chymotrypsin increases the incidence of detachments. In our group of 944 eyes enzyme was used for extractions in 32 per cent of cases and the incidence of aphakic retinal detachment was 5·7 per cent. Shapland (1934), however, quotes an incidence of retinal detachment of 2·2 per cent for extracapsular extractions, and his figures are derived from hospitals historically associated and with similar populations. The essential differences between the philosophy of cataract management and surgical technique in the 1920s and the 1960s are shown in Table XIII. The proportion of high myopia in Shapland's patients and in our series cannot be statistically compared since early figures are not available. While there is no reason to believe that Shapland's figure of 2·2 per cent includes a much lower number of myopes he concluded that there was a high proportion of myopics among cases of aphakic detachment. Hyams and others (1975) give an incidence of 6·7 per cent for myopia above –6·00.

The procedure for cataract extraction in our group did not differ radically from that of others and no cases had prophylactic retinal treatment. Thus high myopia is undoubtedly a cause for concern when cataract extraction is considered. The reports of Schepens (1951) and Hyams and others (1975) confirm this. The finding of Benson, Grand, and Okun (1975) that prophylactic retinal surgery lowers the incidence of aphakic detachment must therefore be heeded. Barraquer (1958) found a higher incidence of detachment among emmetropics because all the high myopes had had precataract extraction scleral resections.

Cataract extraction was bilateral in 5 per cent of our 944 eyes and the incidence of detachment among the bilateral cases was 11·7 per cent. This would be expected as the figure is approximately

Table XII *Visual acuity after retinal surgery in* 62 *eyes*

Acuity	*No. (per cent) of eyes*
HM to CF	25 (40·4)
6/60–6/36	14 (22·5)
6/24–6/18	11 (17·8)
6/12–6/6	12 (19·3)
Total	62 (100)

HM = hand movements; CF = counting fingers

Table XIII *Comparison of management of cases of cataract and of surgical technique in extractions in* 1920*s with those in* 1960*s*

	1920*s*	1960*s*
Time to operate	Mature cataract	Immature to mature
Average age	65 plus	65 minus
Extracapsular	Majority	Minority
Intracapsular	Minority	Majority
Zonulytic enzyme	None	40 per cent
Sutures	0 to 1	2 to 7
Ab. externo incision	None	Over 50 per cent
Cryoextraction	None	55 per cent
Prophylactic retina treatment	None	Minimal
Incidence of detachment	2·2 per cent	5·7 per cent (1967–9)

twice the incidence of unilateral cases (5·7 per cent). Shapland (1961) noted in his series that detachment was commoner in men, and this was so in our series.

According to Hirsch (1964) fewer than 1 per cent of people have degenerative myopia and 15 per cent have myopia of more than −1·00. Sorsby, Sheridan, Leary, and Benjamin (1960) consider that only 3 per cent of younger myopes are outside the range of −4·00 to +6·00. Thus, bearing in mind the crude tolerance of the schematic aphakic eye, our analysis gives a distribution of cases of myopia presenting for cataract extraction of 20 per cent over −5·00 and 7·7 per cent over −10·00. Therefore, using Hirsch's figures, we conclude that the incidence of cataract in degenerative myopia is high, which is a clinically accepted fact.

The incidence of detachment in aphakic myopic eyes may be given in different forms. Thus it can be given for each refractive group or for the whole group. The probability of having a detached retina is 40 per cent for over −10·00 and only 3·5 per cent for emmetropes and low myopes. The incidence of detachment based upon the corrected total becomes 2·3 per cent for emmetropia and up to −4·00, 0·6 per cent for −5·00 and over, and 2·6 per cent for −10·00 to −20·00—a total of 5·5 per cent, which is the total true incidence of detachment for our whole series (Table I). Thus the expected refractions based upon the schematic eye equal the observed findings.

Conclusions

From this study of 944 cataract extractions the following conclusions are drawn.

The incidence of retinal detachment after modern cataract surgery is 5·7 per cent. The incidence of detachment is different in different refractive states, the incidence in cases whose preaphakic refraction is −10 dioptres or more being as high as 40 per cent.

It is also shown that high myopia not only predisposes to aphakic detachment but also to cataract itself.

Evidence is presented that the techniques of extraction do not influence the detachment rate nearly so much as the preoperative refractive state. Nevertheless there does appear to be a greater incidence of aphakic detachment in the current series of cases than in a series reported by Shapland (1934).

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Aetiology of keratoconus

A. G. KARSERAS AND M. RUBEN
From the University Department of Surgery, Welsh National School of Medicine, Cardiff, and the Contact Lens Department, Moorfields Eye Hospital, London

The diverse associations of keratoconus suggest that it is the end result of a number of different pathological processes. It may therefore be regarded as a heterogeneous group of conditions with identical clinical signs but with a varied pathogenesis. The present study is concerned with an analysis of the general medical and psychological associations of 75 keratoconus patients who attended the contact lens department of Moorfields Eye Hospital. Their psychological and behavioural characteristics were studied because Copeman (1965) reported that a number of patients with keratoconus had an 'odd mentality'. Sisters nursing keratoconus patients after corneal grafting had also remarked on the unusual personalities of several of them.

Patients and methods

Data collected in an identical fashion from 75 patients with keratoconus and a control group of 231 randomly selected (one in five) outpatients from the same hospital included (1) sex, (2) age, (3) occupation, (4) history of psychoneurosis, (5) family history of psychoneurosis, (6) completion of the Middlesex Hospital questionnaire, and (7) completion of an analogue scale for the subjective assessment of total life stress.

The Middlesex Hospital questionnaire (MHQ) is an inventory giving a total score for psychoneurotic manifestations based on subscores of anxiety, phobic anxiety, depression, obsessionalism, extrovert qualities commonly associated with hysteria, and somatic symptoms commonly of psychogenic origin. In the analogue scale the patient is asked to mark along a line of 10 digits in proportion to his subjective assessment of life stress.

0 ————————————————————

1 2 1 4 5 6 7 8 9 10

After the first 20 patients in the keratoconus group had been studied particular inquiry was made of the remaining patients about the amount and purpose of eye-rubbing; a history of hay fever, asthma, eczema, or vernal catarrh; and a history of recurrent styes, cysts, blepharitis, or irritating eyes. Subgroups were isolated on a basis of associated systemic or local factors and their MHQ scores compared. All patients were interviewed and assessed for the presence of psychosis or overt psychopathic personality. Twenty keratoconus patients allowed free discussion of a possible association between deviant sexual behaviour and the eyes.

Address for reprints: M. Ruben, FRCS, Contact Lens Department, Moorfields Eye Hospital, High Holborn, London WC1V 7AN

Results

The 75 keratoconus patients resolved themselves into five main groups, comprised as follows.

Group 1, 26 patients with asthma or hay fever. A history of recurrent episodic wheezing or distressed respiration was taken as indicating asthma and seasonal sneezing and itchy eyes as indicating hay fever. Not all of these patients were aware of their clinical status.

Group 2, 14 patients with a dermatological disorder (13 eczema, one psoriasis), of whom 11 also had asthma or hay fever. Thus 37 out of 75 patients gave a history of likely atopy.

Group 3, 10 patients with a history of recurrent styes or cysts or chronically irritable eyes associated with blepharitis. All admitted that they habitually rubbed their eyes.

Group 4, 22 patients with no distinguishing features. Only five volunteered or acknowledged that they rubbed their eyes. They stated that they did so because the eyes were tired or ached.

Group 5, three patients with a family history of keratoconus. In one there was a family history of arachnodactyly and in another a family history of asthma.

Out of the 55 patients closely questioned about eye-rubbing 40 gave a positive response. Some of these denied any personal knowledge of eye-rubbing but remembered mothers or others reprimanding them for it. One patient with eczema denied eye-rubbing or skin-scratching, yet there were obvious scratch marks on facial eczematous lesions.

OTHER FINDINGS

There were more males among the keratoconus group (71 per cent) than among the controls (47 per cent) ($P < 0{\cdot}001$). The mean age ($\pm$SD) of the keratoconus patients was $27{\cdot}3 \pm 8{\cdot}7$ years (oldest 57 years) and that of the controls $46{\cdot}9 \pm 13$ years. As judged by the Registrar General's classification based on occupation, most of the keratoconus patients were from social classes I and II (Fig. 1) whereas half of the total general population was from social class III. There was no significant difference in the number of keratoconus patients and the number of controls with a history of

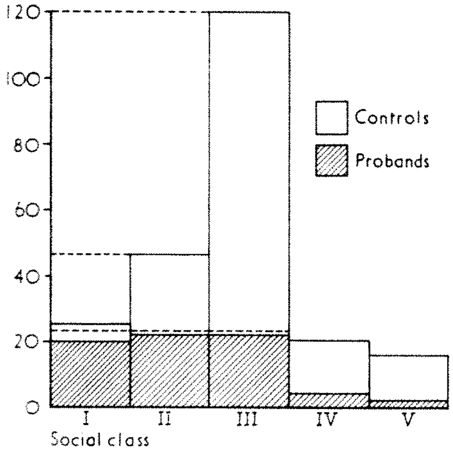

FIG. 1 *Social class of 75 keratoconus patients and of random sample of ophthalmic outpatients*

psychoneurosis. This was assessed from a history of frequent visits to the general practitioner, taking appropriate medicaments, or admission to hospital (χ^2 analysis). By the same criteria there was no significant difference between the number of patients and controls with a family history of psychoneurosis. The average total MHQ score of neuroticism for all the keratoconus patients (three patients with a family history of keratoconus were excluded from this comparison) compared with the total MHQ score of the controls did not reach significance (χ^2 analysis). The value for 'life stress', as assessed by the analogue scale, was lower in the keratoconus patients (3·68, SD 2·24) than in the controls (4·63, SD 2·83) ($P < 0{\cdot}003$). The components of the MHQ—anxiety, depression, phobia, obessionalism, psychosomatism, and hysteria—were subjected to the F-test of significance for each keratoconus patient subgroup. There was no significant difference for any of these variables in the subgroups. In particular, the scores in the idiopathic group 4 were similar to the other subgroups.

Discussion

Keratoconus has been recorded in association with a variety of local and general disorders (Duke-Elder and Leigh, 1965). Many of these may be chance associations with no important pathogenetic implications. The outstanding clinical observation in the present study is the prevalence of atopic conditions. A history of hay fever was elicited in 23 patients (32·6 per cent) and of asthma in 25 patients (33·3 per cent). The incidence of asthma in the general population is in the region of 0·59 per cent (Boland, 1963).

Ridley (1956) first drew attention to the wide variety of atopic conditions associated with keratoconus, and observed that the association was much closer than could be explained by chance. Copeman (1965) also found this. Our study confirms these findings. The incidence of atopy in our patients with keratoconus was much higher than observed by Ridley, but we saw no cases of vernal catarrh as reported by Bietti and Terraboschi (1958). Like Copeman (1965), we found a high incidence of eczema in keratoconus patients. The incidence of keratoconus in asthma and hay fever has not been studied, but clearly it is not an infrequent complication. Brunsting, Reed, and Bair (1955) found that out of 1158 patients with atopic dermatitis six had keratoconus. The 1·5 per 1000 hospital eye patients with keratoconus found by Franceschetti and Caronnes (1960) must be considerably higher than the incidence of keratoconus in an unselected population. The incidence of keratoconus in patients with atopic eczema is thus considerably greater than in the general population.

Within a short time of starting the present study it became clear that many of the patients rubbed their eyes excessively, particularly those with an associated atopic condition. A detailed history of the incidence and nature of eye-rubbing was therefore obtained in the final 55 patients. Forty of them admitted to an abnormal amount of eye-rubbing. Ridley (1961) first noted the prevalence of eye-rubbing in keratoconus and found an incidence of 70 per cent (Ridley, 1966). Rarely severe eye-rubbing in keratoconus patients has been attributed to psychotic behaviour (Ridley, 1966), compulsive rubbing (Copeman, 1965), or a sexual deviation in which the patient experiences sexual gratification on rubbing the eyes (ocular masturbation). Ridley (personal communication) has met the latter once, in a celibate priest who achieved orgasm by rubbing the eyes rather than the prohibited genitalia. True compulsion—where the patient repudiates, unsuccessfully, purposeless eye-rubbing—was not encountered in the present series. Copeman (1965) used the term 'compulsion' in a different sense. Likewise, psychotic or sexual behavioural abnormality was not encountered. Investigation of the latter was limited to 20 patients with whom rapport was sufficiently established to allow free discussion of the possibility of ocular masturbation.

Apparently, therefore, patients with keratoconus who progress to contact lens wear are rarely psychotic, compulsive, or sexually deviant. There may be a higher incidence of these in patients who are unable to wear contact lenses. The selection of patients attending a contact lens department probably explains the absence of mesenchymal syndromes associated with keratoconus in our patients and the absence of Leber's tapeto-retinal degeneration. One-third of the patients with the latter condition, in which eye-rubbing is a common feature, progress to keratoconus (Alström and Olson, 1957). Eye-rubbing is not an overt manifestation of mesenchymal syndromes, although mongols may occasionally be seen to be rubbing their eyes feverishly. It would seem reasonable to suppose that in these conditions the cornea shares in the generalized defect of mesenchyme and stretches as a result of normal intraocular pressures or with normal degrees of eye-rubbing to give keratoconus.

Ridley (1966) suggested that eye-rubbing might be a response to mental stress or emotional tension. These may initiate the habit but we failed to find any persistent psychoneurotic manifestations in our patients from the evidence of the MHQ. The scores of the keratoconus patients were not significantly different from those of the controls. Comparison of the keratoconus patient subgroups for the MHQ scores for anxiety, depression, psychosomatism, obsessionalism, phobia, and hysteria also showed no significant difference. It is noteworthy that the 22 patients in the idiopathic group 4 failed to show any differences in behaviour or psychoneuroticism from those in the other groups when possible dominant aetiological factors could be isolated.

It may be that the idiopathic group 4 in our series belong to group 3 in our proposed classification (see Table). Ridley (1966) found an incidence of 70 per cent of conus posticus in the 30 per cent of keratoconus patients who did not rub their eyes. Such local structural or biochemical anomaly of the cornea may be the dominant aetiological factor in the 'idiopathic' group 4 of the present series and would occupy group 3 of our proposed classification for keratoconus.

The average duration of keratoconus in our patients was 7·1 years. The onset of possible causative eye-rubbing may have been several years before. Persistence of psychoneurosis, if it was an important initiating factor, might be expected if these patients were derived from a background of familial susceptibility to psychoneurosis. However, the incidence of a psychoneurotic history or of a family history of psychoneurosis was similar in the keratoconus patients and the control group. The analogue scale for current life stress was actually lower in the keratoconus group. The present study suggests, therefore, that the current, past, and familial psychoneurotic manifestations of keratoconus patients are within the norm.

At least 50 of our 75 patients had irritable eyes from local or general causes. Probably this irritation acts as a trigger for eye-rubbing in response to the day-to-day stresses of the younger adults of the upper socioeconomic groups. This view is supported by the presentation of a patient subsequent to this study who had bilateral acute keratoconus (Fig. 2). He was an asthmatic studying excessively hard for examinations, and his associated nail-biting in response to stress is seen in Fig. 3. He has been seen to rub his eyes for 10-minute periods under the bilateral pads and bandages that have been applied. Such eye-rubbing could well become habitual and eventually unrelated to a stimulus long after the subsidence of psychoneurotic manifestations.

Table *Proposed classification of keratoconus based on dominant aetiological factor*

Class	*Aetiology*
(1) Eye-rubbing	*(a)* In atopics or bioallergic groups of vernal catarrh, hay fever, eczema, asthma, blepharitis *(b)* Leber's tapeto-retinal degeneration *(c)* Psychogenic-induced eye-rubbing in response to stress or emotional tension *(d)* Habit, to relieve tiredness, accompanying crying, inducing pleasurable phosphenes *(e)* Behavioural abnormality in psychotics, ocular masturbation, ? compulsive states
(2) Generalized mesenchymal defects	Fragilitas ossium Mongolism Erhlers-Danlos syndrome Pseudoxanthoma elasticum Marfan's syndrome
(3) Corneal defects	Conus posticus ? Specific corneal mesenchymal defect
(4) Genetic	Could be via atopy, some of the generalized mesenchymal defects, or corneal defects

Summary

Keratoconus has a common association with atopic conditions. Most keratoconus patients rub their eyes excessively. Eye-rubbing is considered the dominant aetiological factor in two-thirds of patients with keratoconus who progress to contact lens wear. A classification of keratoconus based on the dominant aetiological factors is proposed. No significant psychoneurotic factor was found in the keratoconus patients compared with patients in the control group.

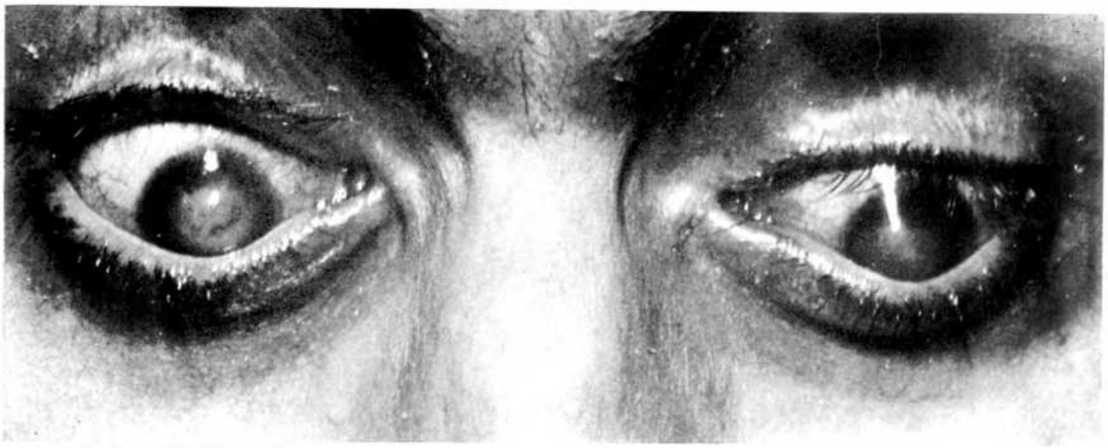

FIG. 2 *Patient with bilateral acute keratoconus*

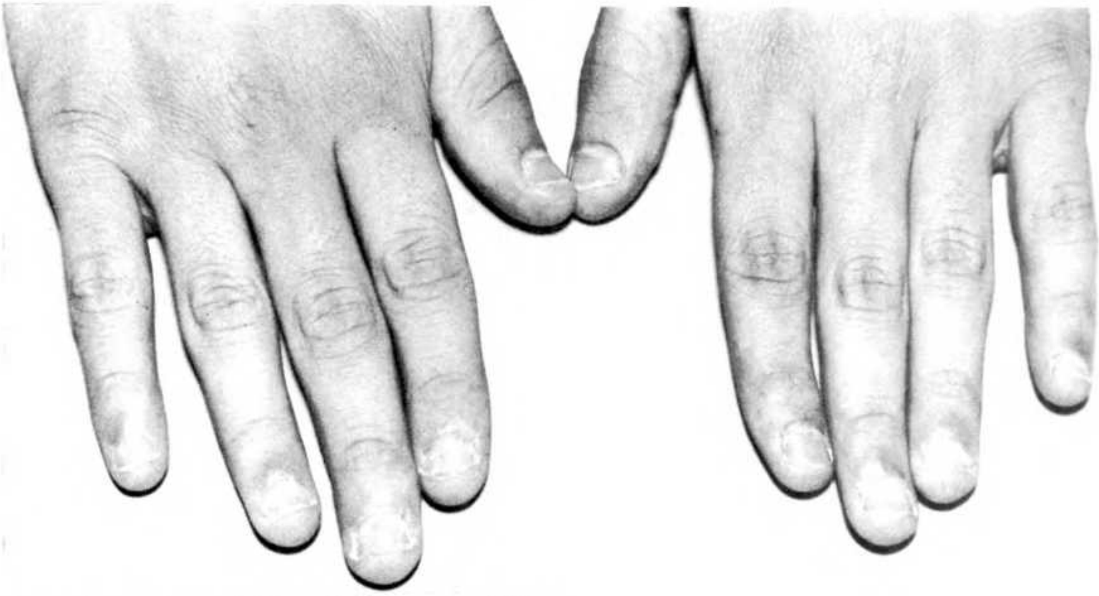

FIG. 3 *Same patient as in Fig. 2 showing severe nail-biting*

We thank Mr K. John and Mr R. G. Newcombe, of the Department of Medical Statistics at the Welsh National School of Medicine, for their help in preparing and analysing the computerized data.

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Corneal changes in patients treated with clofazimine

P.-E. WÅLINDER, L. GIP, AND M. STEMPA
From the Eye and the Dermatological Clinics, Sundsvall's Hospital, Sweden

Clofazimine (Lamprene) is a phenazine derivative (Barry, Belton, Conalty, Denneny, Edward, O'Sullivan, Twomey, and Winder, 1957) which is active against mycobacteria (Vischer, 1969). It has been used in the treatment of leprosy for more than 10 years (Browne, 1965a) and recently it has also been tried in different dermatological diseases including psoriasis and pyoderma gangrenosum (Gip and Stempa, 1976). A common side-effect is a reddish-brown discoloration of the skin (Browne, 1965b), and there have been reports of pigmentation of the conjunctiva (Browne, 1965b, 1969; Schultz, 1972) and of the cornea (Öhman and Wahlberg, 1975), although such changes have also been denied (Imkamp, 1968). The possibility that clofazimine treatment in psoriatic patients causes corneal changes is discussed.

The study comprised 19 patients who were being given clofazimine as a treatment for psoriasis; their mean age was 45 years. The dose was usually 400 mg daily for one to two months. Ocular examinations covered visual acuity, slit-lamp microscopy (Haag-Streit 900 slit lamp using ×10 to 16 ocular) ophthalmoscopy, applanation tonometry, Goldmann perimetry, and colour vision tests. The first ocular examination was performed between two days and two months after the clofazimine therapy had ceased.

Two patients, Cases 1 and 2, showed obvious corneal changes.

CASE 1

A 47-year-old man with psoriasis pustulosa was treated with clofazimine 100–400 mg daily for two months (total dose 20 g). The psoriatic lesions improved, but the skin showed a reddish-brown discoloration which lasted six months after the clofazimine therapy had stopped.

At the first ocular examination two days after the end of the treatment the visual acuity, visual fields, and colour vision were normal. Slit-lamp microscopy revealed several fine brownish, branched lines in the most superficial layers of both corneae (Fig. 1). Sometimes the border of the line was well marked, but at other times the brownish colour merged into the surrounding cornea. Using high magnification (×16 ocular) the lines showed a fine granular appearance. The changes were localized to the lower part of the cornea and there were no epithelial defects. No pigmentation was seen in the deeper layers of the cornea or in the conjunctiva. The lens and fundus were normal except for a very fine granular pigmentation scattered over both macular regions.

Repeated examinations during a one-year follow-up period showed a gradual decrease in the corneal changes. However, at the last examination, a few, very fine, brownish lines could still be seen in both corneae.

CASE 2

A 29-year-old woman with psoriasis pustulosa was treated with clofazimine 100–400 mg daily for two months (total dose 20 g). The psoriatic lesions improved. The patient noted a slight reddish-brown discoloration of the skin and small dry spots on the legs. The discoloration had disappeared two to three months after the end of the treatment but some of the dry spots still remained six months later.

At the first ocular examination two weeks after the end of the treatment the visual acuity, visual fields, and colour vision were normal. The slit-lamp microscopy revealed fine, brownish lines in the superficial layers of both corneae similar to those observed in Case 1 (Fig. 2). The conjunctiva, the deeper corneal layers, the lens, and fundus were normal.

Two months later there was a slight regression of the corneal changes and six months later the corneal lines had disappeared.

Both these patients denied having used any other drugs, for example chloroquine or phenothiazine derivatives.

CASES 3, 4, 5, and 6

In four patients, aged 70, 45, 37, and 32 years, both corneae showed a very fine, brownish line horizontally placed across the lower half at the site for lid closure. Using high magnification the line appeared slightly granular; it resembled a common change in the cornea called the Hudson-Staehli line. Visual acuity, visual fields, and colour vision were normal. At examination six to eight months later the line could hardly be seen in one patient (aged 37) but was unchanged in the other three.

Among the 19 patients in this study were two with

Address for reprints: P.-E. Wålinder, MD, Eye Clinic, Sundsvall's Hospital, 851 86 Sundsvall, Sweden

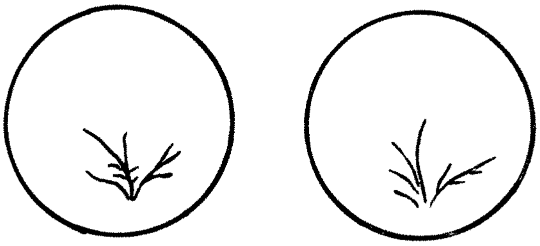

FIG. 1 *Drawing showing corneal changes in Case* 1

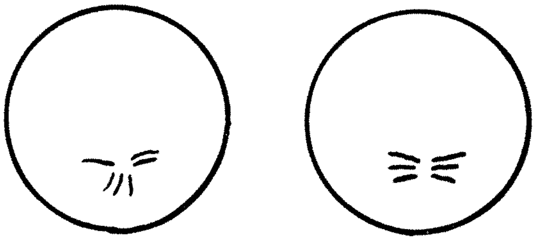

FIG. 2 *Drawing showing corneal changes in Case* 2

known cataracts. Intraocular pressure was normal in all patients except in one with unilateral, secondary glaucoma. Three of the men had defective colour vision but normal visual acuity, visual fields, and fundus. One patient had a brown pigmentation of the conjunctiva similar to a conjunctival naevus. The pigmentation of the conjunctiva was unaltered six months after the treatment had finished.

There were no severe side-effects. Some of the patients showed a marked reddish-brown staining of the skin. Three patients had erythrodermia, and a few complained of nausea and fatigue.

Discussion

There are several kinds of superficial lines in the cornea similar to those observed in the present study. The most common is the Hudson-Staehli line in which iron is deposited in the cornea (Gass, 1964). Corneal lines are also observed after exposure to certain substances, for example, atebrin, and are a well-known complication during treatment with chloroquine and its analogues. In certain corneal diseases there are brownish lines caused by deposition of melanin. The morphological resemblance and possible relationship between these changes are discussed by Bron (1973).

In the present study microscopical examination of 19 psoriatic patients given clofazimine revealed bilateral corneal changes in six cases. Two patients showed between five and 10 brownish, curved lines in the superficial part of both corneae. The changes resembled chloroquine keratopathy except for the brownish colour. None of the patients in this series had used any drugs known to cause corneal opacities nor had they any corneal disease.

The other four patients showed very slight changes, usually there was one brownish corneal line, which it was not possible to differentiate from a Hudson-Staehli line. This line is common in old people, but may be seen by the third and fourth decades (Gass, 1964). The brownish lines in these four patients may thus be a 'normal' finding. However, the fact that in one patient the lines diminished when the clofazimine treatment ended suggests some relationship with the drug.

Eye complications in psoriatic patients are rare. Kerato-conjunctivitis has been described (Horowitz, 1949), but the symptoms and clinical appearance are different from the corneal changes observed in this study.

The excretion of clofazimine has been shown to be very slow in animals (Vischer, 1969). The pigmentation of the skin in humans has been reported to last for a long time (Browne, 1965b), and this is confirmed by one of our patients (Case 1) who had a brown discoloration of the skin which lasted for six months. It is feasible that the skin pigmentation and the corneal pigmentation are of the same origin, thus explaining why the corneal changes in Case 1 persisted for at least one year.

Conjunctival pigmentation has been reported in some lepromatous patients during clofazimine therapy, but was not observed in our study.

There have been no reports of corneal changes in lepromatous patients given clofazimine. The reason may be that the changes are minimal and seen only by microscopical examination. In a study by Imkamp (1968), however, the patients were examined by slit lamp and yet no corneal opacities were found compared to the two cases found in our series. This difference could possibly be due to the fact that Imkamp's patients had been treated mainly with a lower daily dose of clofazimine (100 mg).

Recently, Öhman and Wahlberg (1975) observed brownish lines in the cornea in 10 of 26 patients given clofazimine as treatment for some dermatological disorders. They also found two cases with macular pigmentary changes compared with only one dubious case in our series (Case 1). The clinical appearance and the reversibility of the corneal changes in their series are in agreement with our findings.

Summary

Fine, brownish lines, similar to chloroquine keratopathy, were observed in two of 19 psoriatic patients given clofazimine. There was no functional disturbance and the changes were reversible.

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Clinical manifestations secondary to soft contact lens wear

M. RUBEN, N. BROWN, D. LOBASCHER, J. CHASTON, AND J. MORRIS
From Moorfields Eye Hospital, London

Soft hydrophilic (gel) contact lenses have been in use for a decade since they were introduced by Wichterle, Lim, and Max Dreifus, but their development as a commercial enterprise has taken place only during the past five years. It is now estimated that more than half of new patients being fitted with contact lenses have hydrophilic soft lenses. Statistics were prepared to show the clinical pattern in soft contact lens wear regarding visual acuity, keratometry, state of lids, conjunctivae, cornea, atopy, and contraceptive pill implications. Some data have previously been given (Chaston and Morris, 1975; Brown and Lobascher, 1975; Ruben, 1975; Chaston, 1974). The data have been programmed by computer but the results will be discussed in the light of clinical experience. This report is concerned chiefly with the analysis of clinical data. Data concerning lens behaviour, visual acuity, and wearing patterns were given previously (Chaston, 1974).

Population

A total of 151 volunteers were fitted with five types of hydrophilic soft lenses and studied for one year by ophthalmologists and ophthalmic opticians.

Patients were allowed to wear the lenses for the maximum tolerable times daily; care and disinfection of the lenses were as advised by the manufacturers.

Results

The computer results were based on a data analysis collected over one year and the significance of the results determined by χ^2 fraction $P < 0{\cdot}05$. The details are shown in Tables I to VI.

Of the 151 patients 76 had had previous experience with hard lenses and five of that group wore hard lenses successfully with good daily tolerance. Forty-eight gave a clear history of allergy and 30 had allergies affecting the skin. Forty women out of 106 were taking the contraceptive pill, representing 37·7 per cent (Table I).

Table I *Details of patients*

	No. of patients
Complete records (initial)	151
Complete records (other than initial)	231
Patients with	
previous contact lens wear	50
allergy	32
allergy of skin	20
Patients on pill	26 (as percentage of total) 38 (as percentage of women)
Male to female ratio	3 to 7

Table II *Average wearing time*

	Hours
Women	
on pill	11·3
not on pill	11·3
Yearly average for Schirmer's test	*mm*
women on pill	16·7
women not on pill	18·1
men	18·3

Table III *Corneal tear film*

	Percentage with defects in film continuity
Initial readings	
On pill	19
Not on pill	24
After 12 months	
Men and women (total)	33
Corneal thickness	
On pill	0·55
Not on pill	0·55

The wearing time, as averaged for the whole year, was 11 hours daily to the nearest hour and for those patients not on the pill there was no significant difference (Table II). The yearly average for Schirmer's tears test was 16·7 mm for women on

Address for reprints: M. Ruben, FRCS, Director of Contact Lens Department, Moorfields Eye Hospital, High Holborn, London WC1V 7AN

Table IV *Disease*

Examination	*Lesions (as percentage of total)*	
	PEK	*Blepharitis*
Initial visit	4	33
Three months	27	35
Six months	37	46
One year	43	48

the pill compared with 18·1 mm for women not on the pill, and for men this was 18·3 mm. Thus there is an indication that women on the pill may have a decrease in tear flow.

The precorneal tear film was examined by slit-beam microscope and defects were noted. For women on the pill, 19 per cent were found to have defects compared with 24 per cent of women not on the pill. Whereas for both men and women after one year the figure was 33 per cent (Table III).

Pathological changes in the eye tissues were noted under punctate epithelial keratitis (PEK) alone and with blepharitis; blepharitis and hyperaemia was also correlated over the whole period with the time the lenses had been worn (Table II). The observations were recorded at three-monthly intervals. The prevalence of PEK to the nearest single percentage was 4 per cent initially, with a rapid progression after three months of wear to 27 per cent and at one year to 43 per cent. When correlated with blepharitis it was found that of the PEK group 26 per cent had blepharitis. Blepharitis, itself, was commonly noted: 33 per cent at the initial examination but increasing to 48 per cent after one year's wear.

Hyperaemia of the conjunctivae increased during the whole period of observation (Table IV).

The precorneal tear defects for the whole group (151) were further analysed into the periods of observation. Thus 9 per cent showed defects at the initial visit and by the end of the year 33 per cent showed defects. Tear film defects were noted when dry spot areas (Girard, 1970) were to be seen. Schirmer's tear test when grouped and averaged at the three-monthly visit showed 16·0 mm at initial examination and 19·3 mm at the 12-monthly visit (Table V).

The average corneal thickness (pachymetry) readings in the axis of fixation using a Haag-Streit pachometer showed an initial average reading of 0·54 and after 12 months this was 0·57. When correlated with the wearing pattern it was found that there was not sufficient evidence to suggest any increase in total corneal thickness with increased wearing time. The 20–24-hour wearers were only a group under five in number and the lower readings were not of significance. The gradual overall increase of corneal thickness, however, is of significance (Table VI).

There were other findings that are not easy to present statistically. Thus, while corneal sensation was measured with a Cochet Bonnet anaesthiometer it must be recognized that this is a test that has an inconsistent result. Investigators reported subnormal readings in only 4 per cent (nearest 1 per cent) at the end of the one-year period.

The lens movement on the eye was recorded at each visit but showed no relationship with changes in corneal thickness.

Corneal microcysts are evidence of chronic changes in the superficial cells of the epithelium and initially these were noted in 4 per cent of patients; however, more than 30 per cent had them by the end of the first three-month period of contact lens wear and a final figure of 26 per cent had them at the 12-month examination. Other evidence of disease was epithelial and sub-epithelial

Table V *Precorneal tear film defects (as percentage of whole)*

Examination	*Percentage*
Initial visit	9
Three months	35
Six months	30
One year	33
Skin allergy v. tear film defects	
χ^2	$=5·7662$ $P<0·05$
Other allergy v. tear film defects	
χ^2	$=3·6/65$
Schirmer's test (average)	*mm*
Initial visit	16·0
Three months	18·1
Six months	18·9
One year	19·3
Significant at 5 per cent level	

Table VI *Corneal thickness (average of all readings)*

Examination	*Percentage*
Initial visit	0·54
Three months	0·56
Six months	0·57
One year	0·57
Significant at 1 per cent level	
Corneal thickness and wear pattern	
Hours	
0 to 4	0·56
5 to 9	0·56
10 to 14	0·57
15 to 19	0·56
20 to 24	0·52

punctate keratitis in nine patients; filamentary type keratitis in six, epithelial hypertrophy at upper limbal area in one patient, and stromal oedema with folds in Descemet's membrane in six. Many of these patients had associated lens spoliation and all lesions resolved upon ceasing to wear the lenses. There was no overt case of infective conjunctivitis and all patients used a heat saline method of disinfection. Two patients had recurrent episodes of corneal erosion with soft lens wear that had originated with hard corneal lens lesions.

Discussion

The reason for the significant number of corneal lesions seen at the initial visit (Tables IV and V) in normal adults was that half had had previous hard corneal lens wear experience and at least five patients were still successful wearers.

While a third gave a history of some form of atopy, it was only the skin allergies that showed a positive relationship with eye lesions resulting from soft contact lens wear. The practitioner must therefore be wary of advising long wearing periods in this type of patient.

The contraceptive pill has been blamed for poor contact lens wear but, while this group did show a deficiency of tears, it did not result in lower average wearing times (Table II). Farrell (1973) had also noted this tear deficiency.

This group of patients (151) showed no incidence of bacterial infection with soft lens wear and, while no comparison is possible with a reported incidence of infection being higher in soft lens as compared with hard lens patients (Ruben, 1976) it must be noted that this group was carefully monitored throughout the trial and heat-saline was the chief method for disinfection.

There was an obvious rapid increase in superficial eye lesions even after a few months' wear of soft lenses and this was associated with a slight increase in corneal thickness which did not return to normal even after one year's adaptation. Thus no compensation has occurred.

The incidence of deep corneal lesions, while small in number, is of concern since endothelial decompensation in patients having a latent insufficiency could occur.

Recurrent corneal erosion might be considered a contraindication for wear of soft lenses. But these patients were fitted with conventional soft lenses and not the therapeutic type.

Summary

The study of 151 patients wearing soft hydrophilic lenses for one year revealed no gross irreversible lesions with loss of vision. But of significance was the presence of superficial lesions of the corneal epithelium, and chronic stromal oedema. While no significant loss of wearing time was noted for women taking the pill, the decrease in tear secretion in those patients with a latent dry eye problem could just alter the balance to produce intolerance. From this report it is the long-term changes to the tissues that remain to be fully investigated for soft hydrophilic lenses.

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Subconjunctival and episcleral lipid deposits

F. T. FRAUNFELDER,* A. GARNER, AND T. C. BARRAS
From the External Diseases Unit, Moorfields Eye Hospital, and the Department of Pathology, Institute of Ophthalmology, University of London

Biomicroscopical examination of the peripheral bulbar conjunctiva and episcleral tissue, especially at the level of the palpebral fissure, commonly reveals globules of lipid. The globules vary in size from 30–80 μm in diameter, although in any one individual they tend to be fairly uniform, and were first described by Paliaga (1959) in Italy. A subsequent report from America (Fraunfelder and Hanna, 1975) indicated that the prevalence of the lipid deposits increases with age, over half the population aged 50 years or more in Arkansas being affected. The deposits assume two basic patterns: most often multiple globules lie adjacent to blood vessels but sometimes they occur in small isolated foci. Perivascular distribution is six times more common on the nasal side and twice as common on the temporal side when compared with isolated patches (Fraunfelder and Hanna, 1975).

The purpose of this report is to compare the prevalence of this entity in Great Britain with that observed in the United States of America, to consider its relationship to arcus senilis of the cornea, and to describe the histopathological features.

Patients and methods

From January to July 1975 over 1000 randomly selected outpatients at Moorfields Eye Hospital drawn from various parts of Britain were examined biomicroscopically for the presence of conjunctival or episcleral lipids. Some were also examined for corneal arcus senilis. Patients who had not spent at least three-quarters of their lives in the United Kingdom were excluded from the study. Photographs were taken using a Zeiss photo slit lamp and a macro camera as described by Brown (1970). Twenty-eight eye bank eyes were

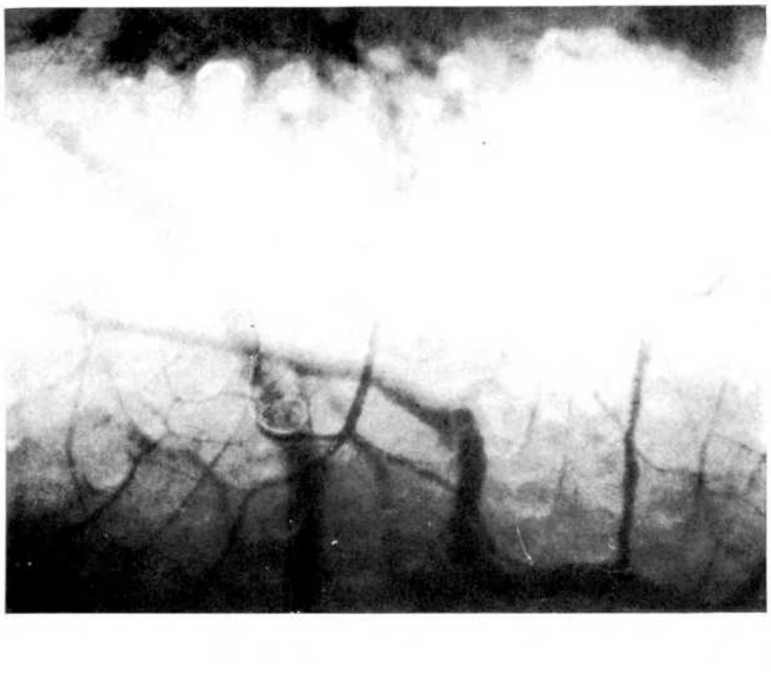

FIG. 1 *Slit-lamp photograph of multiple lipid globules in deep conjunctiva and episclera.* ×11

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*Visiting Professor, Institute of Ophthalmology, July 1974 to July 1975. Present address: Department of Ophthalmology, University of Arkansas Medical Center, 4301 West Markham, Little Rock, Arkansas 72201.

Address for reprints: Dr A. Garner, Institute of Ophthalmology, Judd Street, London WC1H 9QS

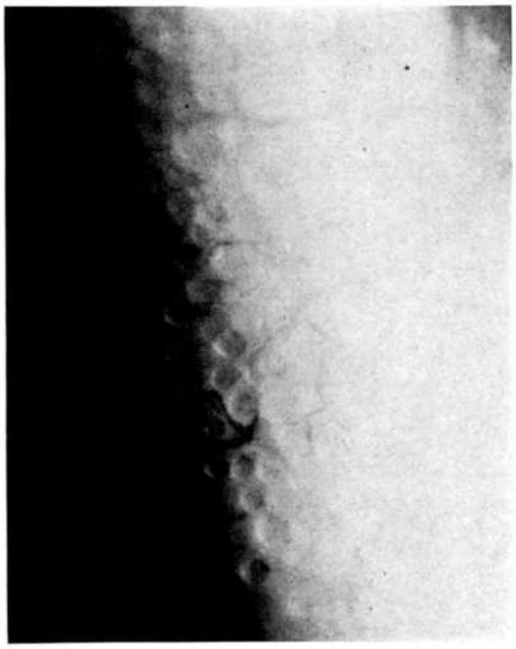

FIG. 2 *Widespread distribution of lipid globules in bulbar conjunctiva of man who had sustained blast injury to both eyes.* ×14

examined histologically, the tissue being fixed in formol saline and variously stained with haematoxylin and eosin, oil red O, osmium tetroxide and α-naphthylamine (OTAN), and by Okamato's method for cholesterol. Carbowax embedding (a water-soluble wax designed to impregnate tissues without requiring the prior removal of lipid) was also performed on selected specimens.

Results

Clear round globules were seen at varying depths within the conjunctiva but predominated in the episcleral tissue (Fig. 1). The deposits were asymptomatic and, although differing in size from patient to patient, were of uniform diameter in a given person. In one patient, who had sustained a blast injury during the second world war, the whole bulbar conjunctiva of both eyes was filled with lipid globules (Fig. 2). The youngest person to show the presence of globules was 21 years old. The prevalence and severity of the lesion increased linearly up to the age of 70 years: beyond this age the prevalence declined (Fig. 3). The proportions of men and women with conjunctival lipid deposits were not significantly different. The prevalence of corneal arcus also increased with age in both sexes (Fig. 4) but without any reduction beyond the age of 70 years, so that the correlation in individual cases between the presence of arcus and conjunctival lipid was not statistically significant.

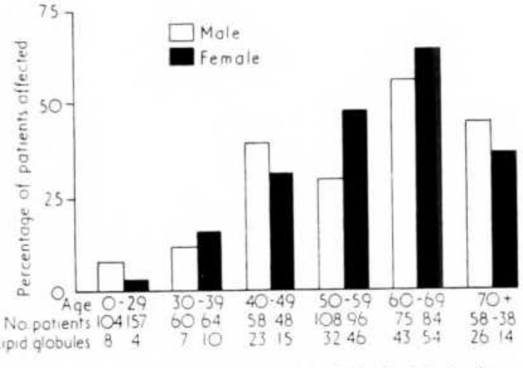

FIG. 3 *Prevalence of subconjunctival lipid globules in Great Britain at different ages in men and women*

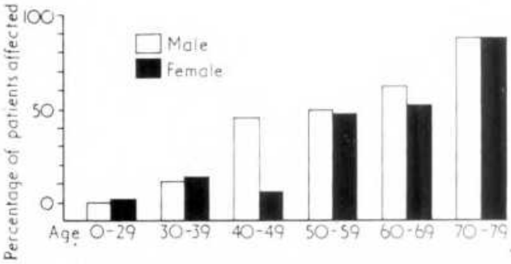

FIG. 4 *Prevalence of corneal arcus in men and women at different ages*

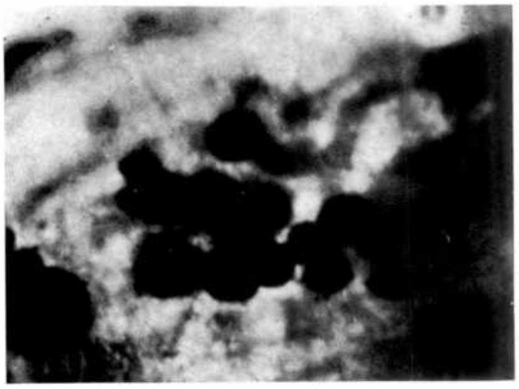

FIG. 5 *Stained subconjunctival globules in intact enucleated globe showed pronounced uptake of oil red O (from colour original).* ×18

Examination of the subconjunctival globules with a dissecting microscope showed a predominantly perivascular distribution, and it was noted that heat generated by the illuminating source caused them to fuse and lose their discrete spherical shape. Treatment of the globules at this stage with oil red O produced an intense uptake of the dye

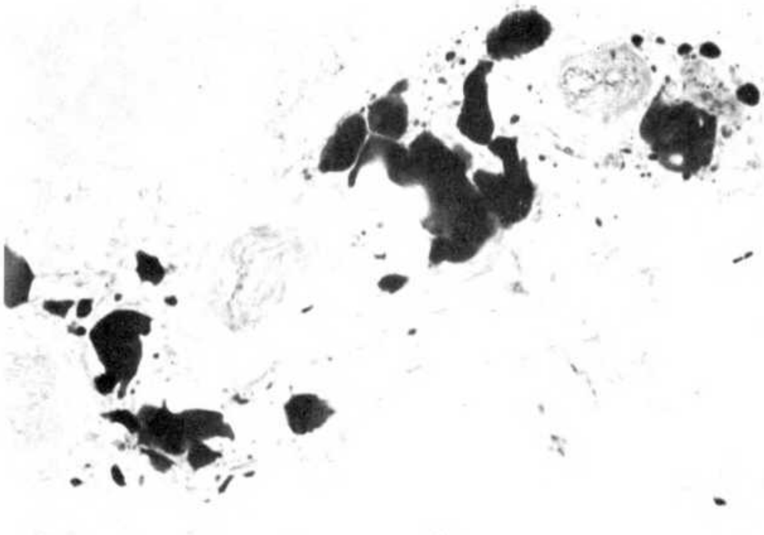

FIG. 6 *Frozen section showing extracellular lipid deposits adjacent to conjunctival blood vessels. Oil red O.* ×90

by the deposits (Fig. 5). Although frozen and carbowax-embedded sections were prepared the lipid globules were seldom retained in the mounted preparation, the rare exceptions showing amorphous fat devoid of any limiting membrane and apparently located within extracellular spaces in the loose connective-tissue of the subconjunctiva and episclera (Fig. 6). Staining for cholesterol by Okamoto's method on the gross specimen resulted in a blue-black reaction product. Finely particulate lipid which stained with oil red O and gave a brown-black colour in the OTAN procedure was demonstrable in the sclera in all cases.

A biopsy specimen, which had been taken some years earlier from the patient demonstrated in Fig. 2, examined in routine paraffin-embedded sections showed fat spaces surrounded by a granulomatous inflammatory reaction (Fig. 7).

Discussion

Conjunctival and episcleral lipid globules are easily missed unless specifically looked for, ideally using either direct or indirect retroillumination. The aggregated globules resemble frog-spawn and occur most often between the loops of large, tortuous blood vessels.

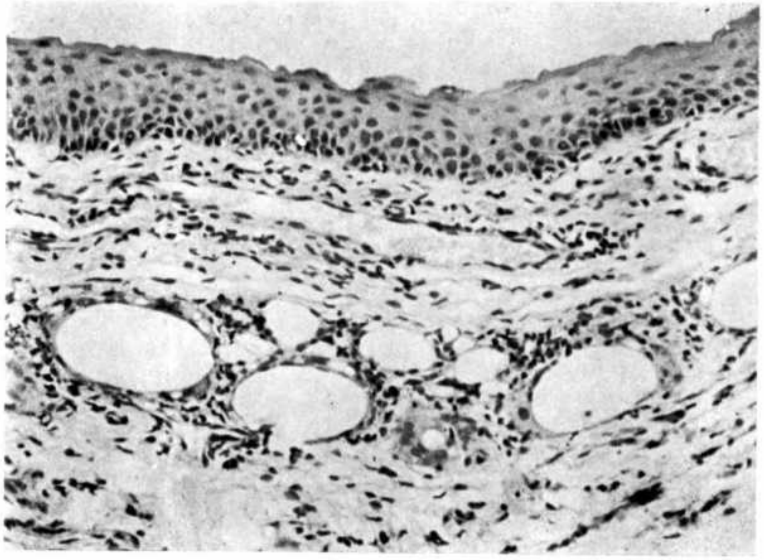

FIG. 7 *Section showing lipid spaces in conjunctival stroma surrounded by giant-cell granulomatous reaction. Haematoxylin and eosin.* ×185

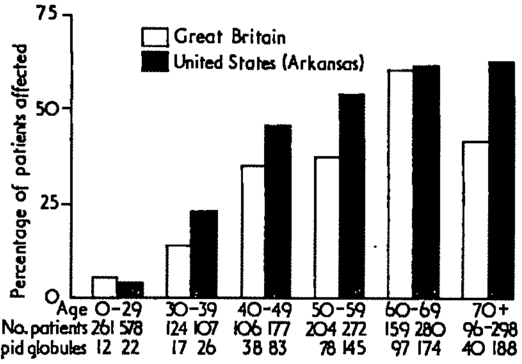

FIG. 8 *Comparative prevalence of subconjunctival lipid globules in Great Britain and United States of America at different ages. (US data from Fraunfelder and Hanna,* 1975)

The prevalence of the condition shows a clear relationship with age. Beyond the age of 70 years, however, the American data show that the rise in prevalence is halted (Fraunfelder and Hanna, 1975), while the present study suggests that it might even be reversed. The American study also showed a preponderance of women with subconjunctival lipid at all ages, but there was no convincing evidence of such a predilection in British subjects. However, the overall prevalence seems to be slightly higher in Arkansas (Fig. 8).

With increasing age lipid accumulates between the collagen fibres of the sclera, particularly towards the uveal surface, and this process may share a common pathogenesis with corneal arcus formation, with which it is commonly associated (Yanoff and Fine, 1975). Consequently, if the subconjunctival globules originate from the same source as those in the sclera—and our finding of scleral lipid deposition in all eyes with conjunctival globules examined histologically lends some support to this hypothesis—a good correlation between the conjunctival lesion and corneal arcus might also have been expected. This, however, was not the case.

The reason for this disparity is not immediately obvious but may be linked with the observation that the lipid deposited in the cornea and sclera is in a finely particulate form, being largely bound to low density lipoprotein (Walton, 1973), whereas that in the loose stroma of the conjunctiva occurs as much larger globules which probably represent unbound fat. There is good evidence that the lipid of corneal arcus senilis is derived from the circulating plasma (Cogan and Kuwabara, 1959; Walton, 1973; Walton and Dunkerley, 1974), and the frequent perivascular and extracellular location of the deposits as well as their cholesterol content are conducive to similar reasoning in respect of the conjunctival lesion. Whether or not the loose structure of the subconjunctival stroma facilitates the fusion of smaller lipid particles, which have seeped through a vascular endothelium subject to an age-related increase in permeability, is not known.

Other possibilities for the origin of the conjunctival globules, referred to in an earlier paper (Fraunfelder and Hanna, 1975), include forward migration of orbital fat, degenerative changes in the tissues, and trauma to the conjunctival blood vessels caused by eye movements and blinking. The essentially extracellular location of the lipid droplets, however, lends little support to any but the last of these suggestions. The extent to which leakage of circulating fat might represent a fundamental degenerative change in the conjunctival vessels, after the manner postulated for arteriosclerosis in other sites, or be attributable to repeated episodes of minor trauma is not known, although the finding of massive lipid deposition in the conjunctiva of a man subjected to blast injury suggests that the latter hypothesis is a real possibility.

Fortunately, in view of their high prevalence, conjunctival and anterior episcleral lipid globules almost never give rise to symptoms—the extremely rare exception appearing to be a granulomatous reaction which probably reflects an alteration in the nature of the fat.

Summary

Biomicroscopical examination of the bulbar conjunctiva and anterior episclera of 1000 randomly selected outpatients showed the presence of multiple discrete lipid globules in 30 per cent. The lipid deposits were asymptomatic. Their prevalence was age-related, while their distribution and composition were consistent with origin from the conjunctival blood vessels.

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Vicryl (polyglactin 910) in cataract surgery
A controlled trial

R. S. BARTHOLOMEW, C. I. PHILLIPS, AND C. G. F. MUNTON
From the Department of Ophthalmology, University of Edinburgh, and Princess Alexandra Eye Pavilion, Royal Infirmary, Edinburgh, and the Kent County Ophthalmic and Aural Hospital, Maidstone, Kent

A preliminary study into the use of Vicryl in cataract and squint surgery has already been published (Munton, Phillips, Martin, Bartholomew, and Capperauld, 1974). The safety and efficacy of the material were confirmed and it was concluded that the overall handling characteristics of monofilament Vicryl 8–0 (dyed purple) were superior to monofilament nylon and equal to virgin silk. The sutures were absorbed with minimal inflammatory reaction on average by the 58th postoperative day. The only abnormalities which were possibly attributable to the new suture were three drainage blebs in cataract sections, two of which disappeared spontaneously.

The purpose of this prospective, controlled randomized trial on the use of Vicryl in cataract surgery was to investigate further the possibility of a lack of wound security as a cause of draining blebs—an undesirable and occasionally dangerous complication—and to compare other early and late complications.

Material and methods

Vicryl (Ethicon) was supplied in lengths of 45–73 cm and diameter of 8–0 monofilament and was coloured violet, with one 6 mm curved spatulate needle at each end.

Patients with cataracts were taken without preselection from the waiting lists of the surgeons concerned and randomly (by coin tossing) allotted to the Vicryl or control groups. Unfortunately, numbers were limited by availability of suture material.

Surgeon A used an ab-externo incision and cryoextraction and 4–5 interrupted 10–0 monofilament nylon or Vicryl sutures (18 eyes). Surgeon B used an ab-externo incision, chymotrypsin and forceps extraction, and 5–7 interrupted virgin silk or Vicryl sutures (22 eyes). Surgeon C used a Graefe section with one interrupted and one continuous suture, either Vicryl or monofilament nylon (five eyes).

There had been some difficulty in knot tying during the preliminary study. The initial double throw of Vicryl holds the suture at the required tension, the second (single) throw rucks up the first (double) throw, thereby tightening the knot further. Practice is required to judge the correct tension needed on the first (double) throw if the final knot is not to be too tight. The third and final (single) throw then locks the knot.

Results

Details of the patients are shown in Table I and the complications in Table II.

Early complications, defined as shallow anterior chambers, draining blebs, choroidal detachment, and hyphaema, occurring during the first postoperative week—possibly attributable to the difficulty in knot tying and therefore to wound closure—were found in four out of 26 (15·4 per cent) of the Vicryl group while there were no complications in the control group of 19 patients. The difference, however, was not significant ($\chi^2 = 1{\cdot}5$; $0{\cdot}3 > P > 0{\cdot}2$; $n = 1$).

Late complications, defined as draining blebs present and persisting two weeks after operation—possibly attributable to the new sutures—were found in five out of 26 (19·2 per cent) of the Vicryl group, compared with two out of 19 (10·5 per cent) in the control group—not a significantly different proportion ($\chi^2 = 0{\cdot}07$; $P > 0{\cdot}5$; $n = 1$).

Suture absorption occurred between 30 and 120 days (average 56 days) after operation. The operation on the patient in whom the sutures had disappeared by the 30th day had been complicated by rupture of the vitreous face and severe postoperative iritis. The draining blebs in the remaining patients closed spontaneously without further complication except for one in whom the bleb was freely draining nine months later.

Late hypertrophy in the wound areas was not seen during the 3- to 12-month postoperative period.

The χ^2 test with Yates's modification was used to determine the significance of difference between the Vicryl and control groups.

Discussion

This trial confirmed that the handling characteristics of 8–0 monofilament Vicryl are equal to or better than 10–0 monofilament nylon and equal to 8–0 virgin silk when used as an interrupted or continu-

Address for reprints: R. S. Bartholomew, Department of Ophthalmology, the Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA

Table I *Results obtained by 3 surgeons in 45 cataract extractions*

	Vicryl				*Control sutures*			
Surgeon	*Operations*	*Suture*	*Comments*	*Follow-up*	*Operations*	*Suture*	*Comments*	*Follow-up*
A	11	4–5 interrupted	1 hyphaema 2 shallow anterior chambers 1 draining bleb lasting 1/12	1 year	7	10–0 monofilament nylon interrupted 4–5	1 small draining bleb for 1/12	1 year
B	11	5–7 interrupted	4 draining blebs lasting: 2 weeks 2 weeks 4 weeks 9 months 1 choroidal detachment	1 year	11	8–0 virgin silk 5–7 interrupted	1 draining bleb lasting 4 weeks	1 year
C	4	1 interrupted 1 continuous 10–13 loops	1 hyphaema 1 iritis	2–4 months	1	10–0 monofilament nylon 1 interrupted continuous 10–13 loops	Nil	4 months

Table II *Complications in 45 cataract extractions*

	Suture	
Complication	*Vicryl*	*Control*
	($n = 26$)	($n = 19$)
Draining blebs	5	2
Hyphaemas	2	—
Shallow anterior chamber	1	—
Choroidal detachment	1	—
Iritis	2	—
Early complications	4	—*
Late complications	5	2†

*Difference: $\chi^2 = 1{\cdot}5$; $0{\cdot}3 > P > 0{\cdot}2$

†Difference: $\chi^2 = 0{\cdot}07$; $P > 0{\cdot}5$

ous suture. Knot tying, even with the modified technique described, is not so satisfactory as with 8–0 virgin silk.

The early complications of wound closure might be attributable to this difficulty in knot tying, the incidence being higher in the Vicryl (15·4 per cent) than in the control group (0 per cent). However, these differences were not significant ($\chi^2 = 1{\cdot}5$; $P > 0{\cdot}2$). More experience might well eliminate the problem. A very much larger sample would be required to settle the question statistically. Even had this been practicable in our trial the supply of Vicryl became temporarily suspended.

Late complications—draining blebs present two weeks after operation—may be attributable to inadequate wound closure, as described above, but may also be due to too early suture dissolution. Small draining blebs are not uncommon after cataract surgery, if looked for, but seldom persist for more than four to six weeks. A permanent bleb must be considered an undesirable complication, possibly associated with increased astigmatism and certainly associated with the potential dangers of hypotony and intraocular infections (except in cases of glaucoma complicated by cataract, in which these risks are justifiably taken).

When experimentally implanted into rat muscle Vicryl is absorbed by hydrolysis in about 80 days, while tensile strength, although retained for 30 days, tends to be zero at this time (Capperauld, 1971, 1973). Polyglycolic acid sutures are thought to be retained for a long time in human subcutaneous tissue (Watts, 1975). In the eye, sutures can be seen beneath the conjunctiva, and they had disappeared on average by the 56th postoperative day in our cases. In one patient they had entirely disappeared by the 30th day, and this was of particular interest because it showed that quicker hydrolysis may occur in an actively red eye with greater than normal inflammatory reaction, higher temperature, and blood flow.

Disappearance of sutures from the corneo-scleral wound at this relatively early stage is not ideal in a situation where a corneal wound (in rabbits) has regained only some 30 per cent of the intact corneal strength (Condon and Hill, 1973). No information on limbal wounds is available. Despite these considerations, however, we did not find a significantly higher incidence of late complications. Early suture absorption does not thus appear to be an important factor in this series.

We inspected the corneo-scleral wounds 3 to 12 months postoperatively in view of the observation that intracuticular polyglycolic acid sutures cause late hypertrophy after three months in 50 per cent of skin wounds (Cox and Simpson, 1975). We saw no hypertrophy, however, which agrees with experimental observations on Vicryl (Capperauld, 1973).

Summary

In a controlled, randomized trial in 45 cataract operations a new synthetic absorbable suture (8–0 monofilament Vicryl, made by Ethicon), was compared with monofilament nylon or virgin silk normally used. There was a higher incidence of early complications—hyphaema, shallow anterior chamber, and choroidal detachment (15·4 per cent *v.* 0 per cent)—with the absorbable suture. But these differences were not significant at the 0·05 level and might well disappear with more operative experience, particularly the modified technique of knot-tying.

In handling qualities Vicryl was superior to both 10–0 monofilament nylon and 8–0 virgin silk with the exception of knot-tying, in which it was inferior to 8–0 virgin silk. Vicryl is considered to be a useful absorbable suture in cataract surgery but knot-tying requires modification of technique.

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Recurrence of astrocytoma of optic nerve after 48 years

JOAN MULLANEY, J. WALSH, W. R. LEE, AND J. H. ADAMS
From the National Ophthalmic Pathology Laboratory of Ireland, Royal Victoria Eye and Ear Hospital, Dublin, and University Departments of Ophthalmology and Neuropathology, Glasgow

Hoyt and Baghdassarian (1969) and Spencer (1972), from comprehensive studies of the clinical and pathological features of optic nerve gliomas in childhood, concluded that these tumours are congenital and non-neoplastic and are often associated with neurofibromatosis. Although they may enlarge and cause symptoms in early life they tend to be clinically indolent and self-limiting. This does not apply to every case, however, and Spencer (1972) reported a benign optic nerve astrocytoma in an 11-year-old boy in whom there were four recurrences in the subsequent 13-year period.

Optic nerve gliomas in adults, on the other hand, are aggressive and often rapidly fatal. They may initially simulate optic neuritis, since they usually present acutely (Martin and Cushing, 1923; Sæbø, 1949; Mattson and Peterson, 1966; Hamilton, Garner, Tripathi, and Sanders, 1973; Hoyt, Meshel, Lessell, Schatz, and Suckling, 1973). A pilocytic astrocytoma with some anaplastic features in the optic nerve of a middle-aged patient is therefore of interest. The tumour appeared 48 years after the excision of a juvenile optic nerve glioma.

Case report

In 1925 a 4-year-old boy presented with a left proptosis and defective upward and outward movement of the eye. The exophthalmometer reading was 18 mm on the left and 15 mm on the right. The media were clear and secondary optic atrophy and venous congestion were observed. Radiological examination of the orbit and the Wassermann reaction were both negative. A Krönlein operation was performed and an optic nerve tumour removed by dividing the nerve close to the globe and to the optic foramen. The case was reported by Goulding (1927). The pathological findings were described as follows. 'On macroscopic examination a growth was adherent to the optic nerve and microscopic examination showed fibromatous tissue in which large areas were in a degenerate condition, as evidenced by feebler staining'. The slides are not now available.

In July 1973 the patient, then aged 52 years, presented with a history of gross left proptosis for many years and a large medial orbital mass (right eye 6/6; left eye no perception of light). Radiological studies showed changes which suggested an old lateral orbital fracture. There was no evidence of neurofibromatosis. The left eye was enucleated and a large encapsulated retrobulbar tumour, filling the orbit, was removed. The chiasma was not involved. There was no evidence of recurrence 27 months after operation.

PATHOLOGY

The left eye measured 24×23×23 mm. The optic nerve had been cut flush with the globe. The eye was diffusely atrophic and a temporal crescent was present at the disc. Microscopy showed an old healed keratitis with calcification, generalized optic atrophy, and gliosis and calcification in the region of the papilla. The optic nerve remnants contained sparse but identifiable nerve fibres in hyalinized tissue, the stump being partially covered by ectopic conjunctival epithelium (Fig. 1). The mass in the orbit measured 4·3×4·0×3·8 cm and was apparently encapsulated. On section most of the tumour was solid and of a pinkish-beige colour but there were some small cysts and possible foci of necrosis (Fig. 2).

HISTOLOGY

Some parts of the tumour were composed of trabeculae of greatly elongated pilocytic cells many of which had abundant eosinophilic ectoplasm (Fig. 3*a*). Other areas, some surrounded by these trabeculae, were composed of oval or polyhedral cells containing central, slightly hyperchromatic nuclei (Fig. 3*b*); microcystic change was conspicuous in these areas. Throughout the tumour there was a dense but delicate stroma of collagen and reticulin, but in some parts glial fibrils predominated (Fig. 3*c*). There was also a dense collagenous capsule partly infiltrated by tumour cells. The amount of intercellular matrix varied but here and there it was abundant. Discrete cysts were present but there was no frank necrosis. Blood vessels were very numerous but vascular proliferation of the type associated with highly anaplastic glial tumour was not identifiable. There was considerable nuclear pleomorphism throughout the tumour with the formation of some small multinucleate giant cells (Fig. 3*d*), but mitotic figures were not seen. There were several collections of lymphocytes within the tumour.

The appearances were interpreted as those of a pilocytic astrocytoma of the optic nerve which, over many years, had widely infiltrated the orbital tissue, thus

Address for reprints: Joan Mullaney, Royal Victoria Eye and Ear Hospital, Adelaide Road, Dublin 2, Eire

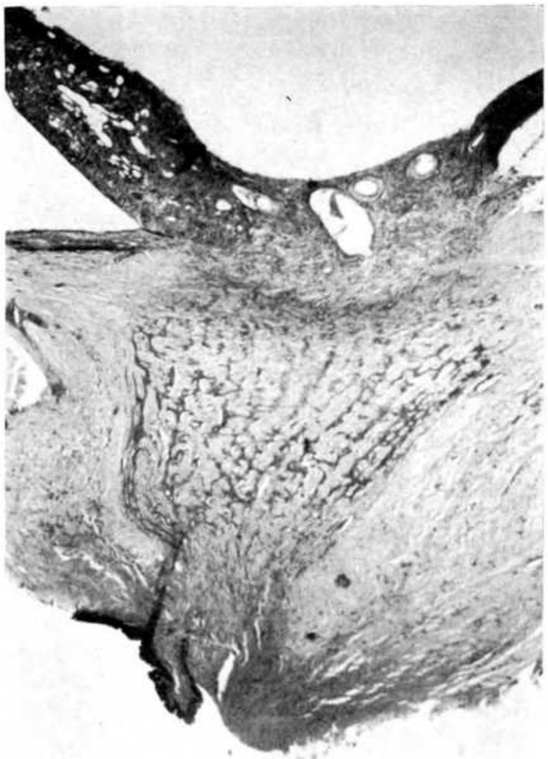

FIG. 1 *Optic nerve and peripapillary retina of enucleated eye showing atrophic nerve and strip of conjunctival epithelium on posterior surface of specimen. Haematoxylin and eosin.* × 25

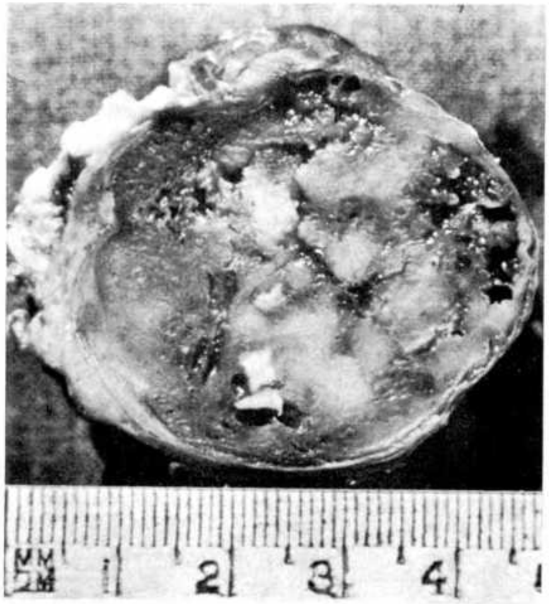

FIG. 2 *Appearance of cut surface of orbital tumour.* × 1·5

acquiring a rich mesenchymal stroma, and was now showing some signs of anaplasia. To confirm this diagnosis some of the formalin-fixed tissue was used for electron microscopy. The tissue was post-fixed in 3 per cent glutaraldehyde and 1 per cent osmium tetroxide and embedded in araldite. Ultrathin sections stained with uranyl acetate and lead citrate were examined in a Philips 300 electron microscope. The preservation of the cell ultrastructure was not ideal but useful information was obtained. Most of the tumour cells were of irregular size and outline (Fig. 4), occasionally multinucleate (Fig. 5*a*), and showed the characteristic feature of astrocytes in that the cytoplasm contained numerous filaments (70–80 Å in diameter), often arranged in dense bundles (Fig. 5*b*). The nuclear chromatin was irregularly dispersed in these cells and the nucleolinema was coarse in the prominent nucleoli. Dense cytoplasmic inclusion bodies and dilated, rough endoplasmic reticulum containing granular material were identified in many of the cells. A few lipid histocytes were seen and other cells, which were either totally degenerate or could not be easily identified, were found between the tumour astrocytes. The capillaries available for examination did not show endothelial proliferation. The extracellular spaces contained collagen bundles, granular material, or debris which sometimes included circular electron-dense structures of about 1 μm diameter. These structures were very similar to those of degenerate lipid bodies.

Discussion

The information available about the nature of the original tumour (Goulding, 1927) is scanty, but most probably the 'growth adherent to the optic nerve' composed of 'fibromatous tissue and large degenerate areas' was a typical optic nerve glioma of childhood type. Examination of the enucleated eye showed undoubtedly that the orbital part of the optic nerve had been totally removed and that there was a large recurrent tumour in the orbit. The tumour had certain atypical features, presumably related to its duration and the extensive infiltration of the orbital tissues, but there was general agreement about its nature (see acknowledgement). The diagnosis of astrocytoma was confirmed by electron microscopy despite the fact that all of the tissue had originally been fixed in 10 per cent formalin. This showed that the principal cells had ultrastructural characteristics similar to those described as tumour astrocytes in juvenile gliomas (Luse 1961; Anderson and Spencer, 1970), in an adult malignant glioma (Hamilton and others, 1973), and in an optic tract glioma and a glioblastoma multiforme (Raimondi, Mullan, and Evans, 1962). Malignancy is difficult to assess from cell ultrastructure, but the irregular dispersion of nuclear chromatin, the alterations in nucleolar architecture, and the presence of multinucleate cells are generally considered to indicate dedifferentiation.

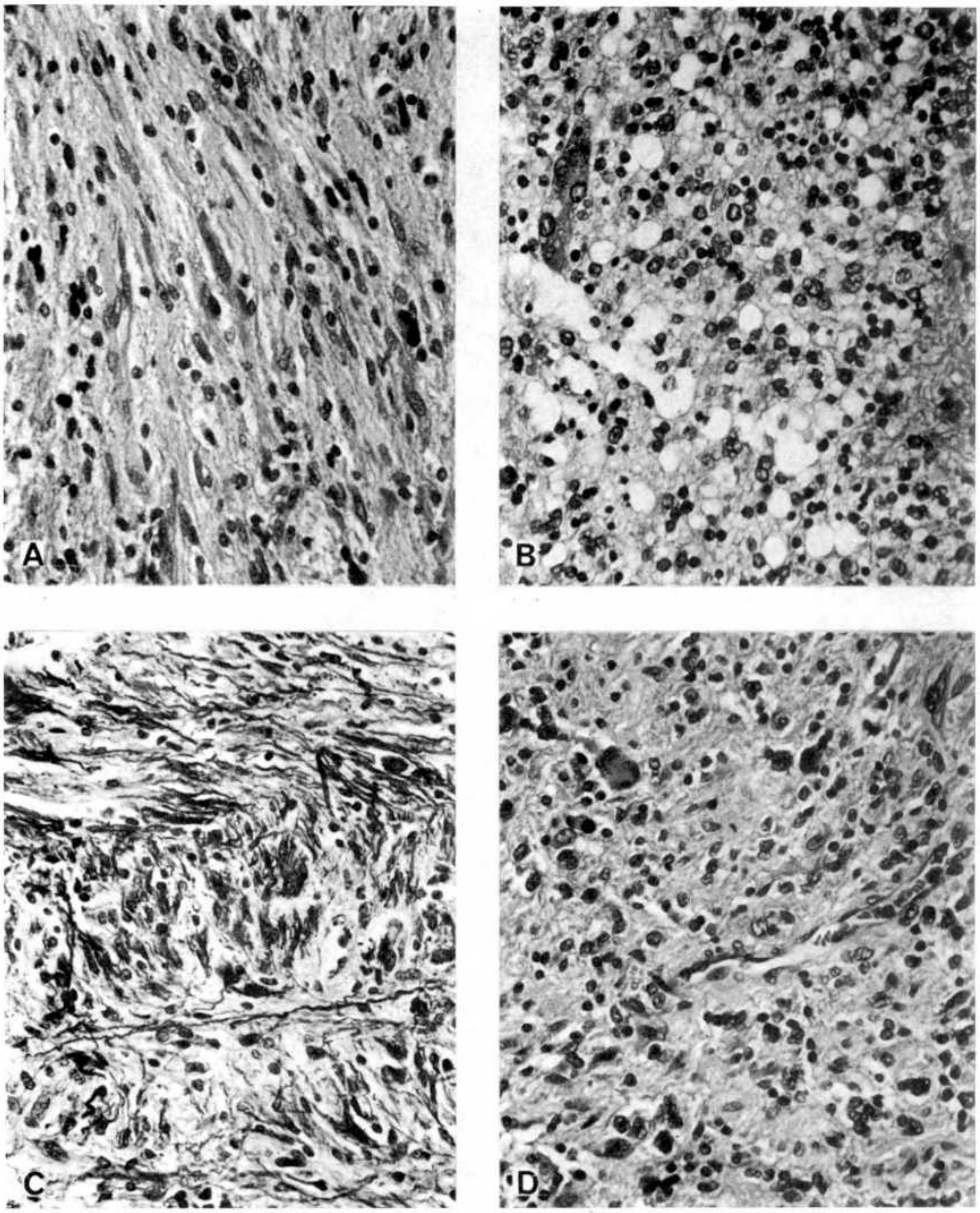

FIG. 3 *Histological features of orbital tumour.* (a) *Area in which pilocytic cells predominate. Haematoxylin and eosin.* ×250. (b) *Microcystic degeneration. Haematoxylin and eosin.* ×250. (c) *Conspicuous glial filaments. PTAH.* ×250. (d) *Cellular pleomorphism and multinucleate cells. Haematoxylin and eosin.* ×250.

The tumour in this case therefore presents some unusual features, and it is of interest to speculate on its origin. The second growth could have arisen in gliomatous residue in the proximal optic nerve or, if excision had been complete, it could have been proliferation from a hamartomatous focus

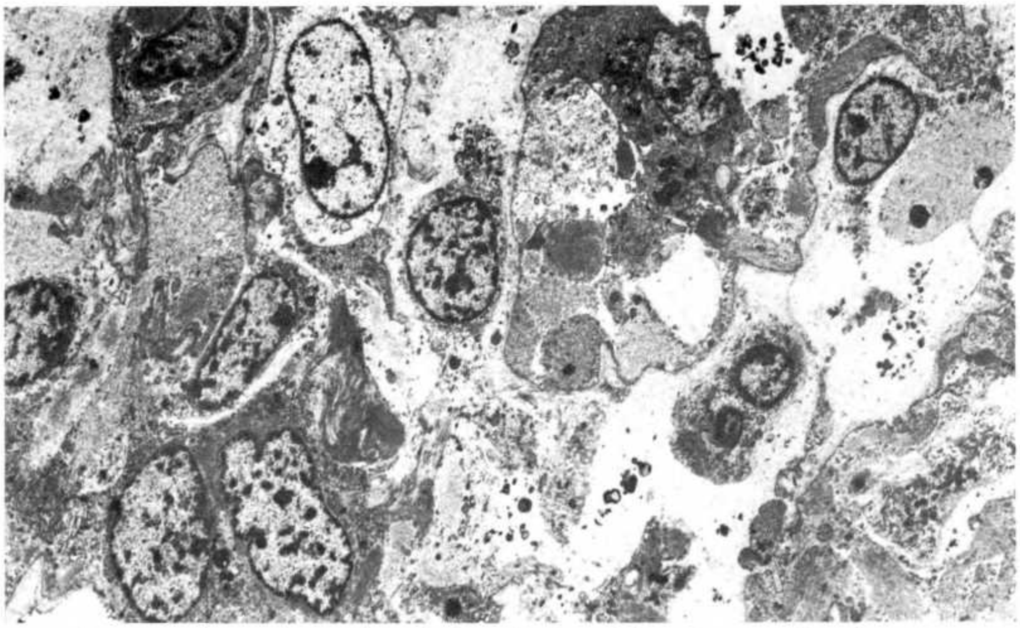

FIG. 4 *Low-power electron micrograph showing irregular size and shape of tumour cells and uneven distribution of nuclear chromatin.* ×2200

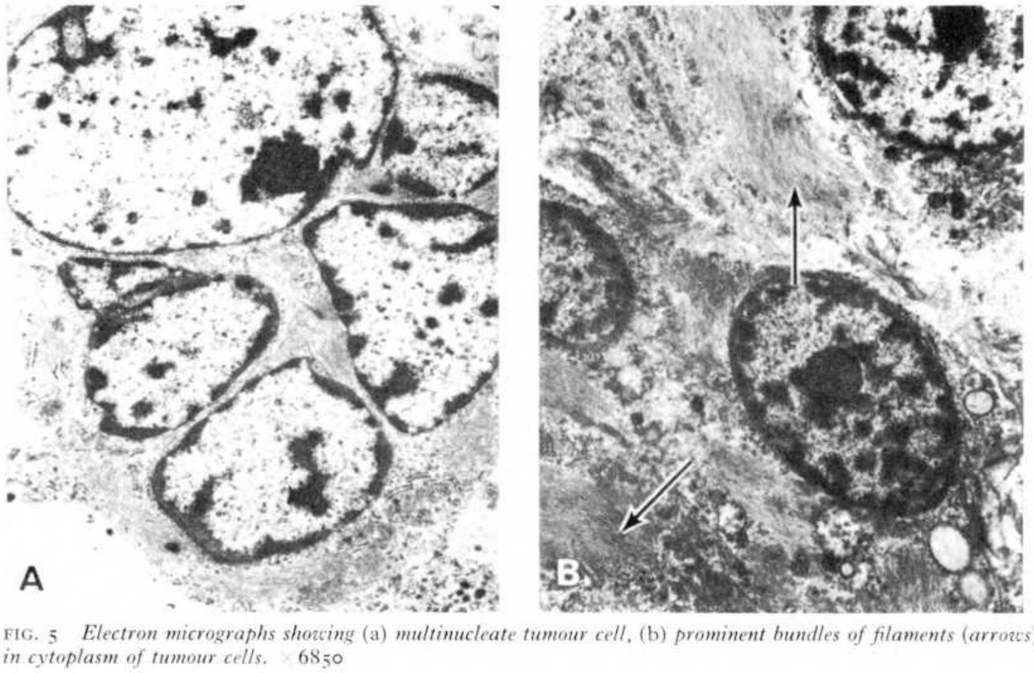

FIG. 5 *Electron micrographs showing* (a) *multinucleate tumour cell,* (b) *prominent bundles of filaments* (*arrows*) *in cytoplasm of tumour cells.* ×6850

in this part of the optic nerve. The latter would have been more likely if there had been clinical evidence of neurofibromatosis. Another potential focus for neoplastic transformation could have been collateral hyperplasia of the glial cell component in the remaining optic nerve segment (Verhoeff, 1932; Anderson and Spencer, 1970). It is unfortunate that the primary tumour was not available for examination, because the case raises the possibility that juvenile gliomata can become malignant. The satisfactory subsequent course after secondary excision is atypical if the second optic nerve tumour is regarded as a glioma of the adult type, although long survival periods have been recorded in two adult optic nerve gliomas (Pagenstecher, 1902; Hoyt and Baghdassarian, 1969), which were first diagnosed at the ages of 30 and 25 years respectively.

Summary

A tumour presumed to be a juvenile glioma of the optic nerve was removed by a Krönlein procedure from a 4-year-old boy in 1925. In 1973 a severe proptosis made it necessary to remove the atrophic eye and a large retro-ocular tumour. Histological examination, supported by electron microscopy, showed the second tumour to be an anaplastic pilocytic astrocytoma. The possible histogenesis and this unusual behaviour pattern are discussed.

We thank Professor Norman Ashton, Dr L. E. Zimmerman, and Professor Dorothy S. Russell for their comments on the orbital tumour, Mr R. Lester for technical assistance, and Miss Patricia Murphy for secretarial aid.

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Book reviews

Chromosomal Aberrations in Ophthalmology. By J. FRANÇOIS, R. BERGER, and H. SARAUX. 1975. Pp. 504, 245 figs, 15 tables, refs. Van Gorcum, Assen/Amsterdam (225·00 D.fl.)

In 1972 the Annual Report to the Société Française d'ophtalmologie, *Les Aberrations Chromosomiques en Ophtalmologie,* appeared and has become the standard work on cytogenetics and ophthalmology. This translation is essentially that of the original work, except for the first part on the elements of cytogenetics which has been revised to include the new techniques of chromosome banding. Regrettably, but understandably, the main chapters which are devoted to detailed descriptions of ophthalmic abnormalities associated with chromosomal anomalies have not been up-dated. The book is lavishly illustrated and has an exhaustive bibliography.

While this edition, in which the translation into English is adequate, is an admirable work of reference and will be a model of its kind for many years, the original is to be recommended to all those with a good knowledge of French. BARRIE JAY

Concussive and Penetrating Injuries of the Globe and Optic Nerve. By T. E. RUNYAN. 1975. Pp. 221, figs, refs. Mosby, St Louis; Kimpton, London (£16·25)

This is a comprehensive and well-written account of ocular trauma and its management. The text, which is arranged anatomically, is enhanced by the frequent use of short case histories and the illustrations and diagrams (by the author himself) are first class. In the more controversial areas, such as the management of hyphaema, there is a more detailed discussion and appraisal of the recent literature but in many fields, such as the surgical treatment of traumatic cataract, the author draws upon his own experience. Here he favours the intracapsular approach in young adults. The last chapter, on diagnostic techniques, is a useful conclusion to a book which although expensive deserves a place in the ophthalmic library. R. COAKES

Current Medical Treatment, 4th ed. By C. W. H. HAVARD. 1976. Pp. 783, refs. Wright, Bristol (£10)

Nearly one half of prescriptions today are for drugs which did not exist five years ago. Hence the need for *Current Medical Treatment.* Chapter 21 on diseases of the eye is written by John Dobree and as one would expect it is a gem of sparkling compression.

It is impossible of course to write a textbook on medical treatment without reference to disease and one of the striking and most useful aspects of this book is the introduction to the syndrome under discussion because therein often lies the briefest summary of the significant and important features. Such pronouncements are most valuable to the specialist so absorbed by his own particular problem that he is unable to sort out the wheat from the chaff of other disciplines.

An ophthalmologist reading through these pages cannot but fail to note an ophthalmic aspect to the majority of medical diseases. Most organisms and many viruses affect the eye, a large number of drugs have secondary ocular effects, the endocrine and haemopoetic systems have their ophthalmic complications and neurological disease can hardly help offending either the sensory or motor ocular system. These ophthalmic overtones make *Current Medical Treatment* almost compulsive reading for the lively ophthalmologist who cares to open its covers and, as a source of reference in therapeutics, this text must surely be in a class of its own. S. J. H. MILLER

Introducing WHO. 1976. Pp. 88, figs. World Health Organization, Geneva (Sw.fr.10)

A paperback production of what is now the standard periodical size. This profusely illustrated and highly informative volume will serve a useful purpose in many fields, for WHO is an organization which tends in some quarters to be taken for granted and then ignored. A foreword by the Director General, Dr Halfdun Mahler, is followed by an account of the origin and development of international health co-operation, a description of the nature and structure of WHO, and of the scope of its activities, a subject amplified in a later section. The prevention and control of specific diseases and the methods of work of the organization are fully treated; inevitably the budgeting and administration sides are described. Annexes give notes on publications and documents, and addresses of associated bodies. This book will be most welcome to those who want to know more—or indeed—all about the WHO.

A list of addresses of suppliers of WHO publications throughout the world is appended; in this country they may be obtained from HM Stationery Office, 49 High Holborn, London WC1V 6HB, as well as from the listed addresses in many other cities. F. W. LAW

L'Année Thérapeutique et Clinique en Ophtalmologie. International Congress of Ophthalmology. 1974. Pp. 701, figs, tables, refs. Libraire Fiieri, Lamy, Marseille (no price given)

This interesting book contains, presumably in some cases in a shortened form but including numerous illustrations, a large number of communications published at various meetings and symposia in France during 1974. The papers are in several languages but French and English predominate.

There is full coverage of the International Symposium on the Visual Field (in fact this section occupies most of the book) and there is an account of the Symposium on Ophthalmic Education.

The book is of a general interest but is particularly important to those concerned with perimetry or with ophthalmic teaching. REDMOND SMITH

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Correspondence

Diathermy machines

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, There must be a very large number of diathermy machines lying idle in Eye Departments all over the country since cryotherapy is now almost exclusively used for retinal detachment surgery.

May I suggest that these machines can be used as a substitute for cautery for small surface bleeding points for all types of operations. The medium point adjustable applicator seems the best and this unipolar applicator is more accurate and just as easy to use as the bipolar type of diathermy such as the Codman Mentor.

Speaking from a standpoint of little knowledge (which I hope is not too dangerous a thing) having designed a simple diathermy machine (1958), there would appear to be no danger of retinal damage as the current is small and the duration of contact short.

There is the obvious disadvantage of having another bulky instrument in the theatre and attaching a pad to the patient but coagulation of bleeding points appears to be satisfactory and positive.

Yours faithfully,
J. GIBSON MOORE

Barnet Area Health Authority,
Edgware General Hospital,
Edgware,
Middlesex, HA8 OAD
20 *July* 1976

Reference

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Notes

European Ophthalmic Pathology Society

The European Ophthalmic Pathology Society held its 15th annual meeting as a joint meeting with the Verhoeff Society in Washington DC, from 25 to 29 April 1976.

The scientific sessions were held at the Armed Forces Institute of Pathology and were organized by Lorenz E. Zimmerman, Head of the Ophthalmic Pathology Branch, the Armed Forces Institute of Pathology, and his staff.

A sight-seeing tour was arranged for the European participants on Sunday 25 April, followed by a reception in the evening at the Mayflower Hotel.

A concert was given by the National Symphony Orchestra in the concert hall of the famous Kennedy Centre on the Tuesday night, and a reception and banquet took place in the Presidential Room of the Mayflower Hotel on Wednesday 28 April 1976.

The next meeting of the European Ophthalmic Pathology Society will be held in Munich, West Germany, in June 1977, when Professor Otto-Erik Lund will be the Organizing Secretary.

Symposium on Colour Education

Renfrew, Scotland, 1 and 2 October 1976

A symposium on colour education will be held at the Normandy Hotel, Renfrew. It will include papers on aspects of the use of colour in education for teachers and educationalists in addition to papers covering the basic principles of colour science and language and technology for artists, designers, and colour technologists.

Further details and application forms for registration may be obtained from the Hon. Secretary of the Colour Group (Great Britain) (Scottish Section): Dr A. R. Hill, Glasgow College of Technology, Department of Ophthalmic Optics, North Hanover Place, Glasgow G4 OBA.

Course in Contact Lens Technology

Houston, Texas, 2 to 4 December 1976

The Department of Ophthalmology, Baylor College of Medicine, Houston, Texas, announces its annual course in contact lens technology.

The course is open to all ophthalmologists, residents in ophthalmology, and technicians sponsored by an ophthalmologist. Attendance is limited to enable participation in the practical sessions by all participants. For further information write to David Paton, MD, Professor and Chairman, Department of Ophthalmology, Baylor College of Medicine, 1200 Moursund, Houston, Texas 77025, USA.

Course in Neuro-Ophthalmology

Miami Beach, 4 *to* 7 *January* 1977

The annual course in neuro-ophthalmology will be held at the Doral Beach Hotel, Miami Beach, Florida. The following topics will be emphasized: cerebrovascular disease; computerized axial tomography in neuro-ophthalmology; anatomy and diseases of the parasellar area. Clinical case material will be presented for general discussion, and question-and-answer sessions will invite audience participation. Registrants may submit short free-papers by 15 November 1976 on clinical subjects.

Further information may be obtained from the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, PO Box 520875, Miami, Florida 33152, USA.

Midwinter Seminar in Ophthalmology

Miami Beach, 31 *January to* 2 *February* 1977

The 32nd annual seminar in ophthalmology will be held at the Americana Hotel, Miami Beach, Florida. The main topic will be glaucoma.

It is to be co-sponsored by the University of Florida College of Medicine (Gainesville), the University of Miami School of Medicine (Miami), and the University of South Florida College of Medicine (Tampa).

Obituary

Norman Patrick Robert Galloway, MB, ChB

N. P. R. Galloway died after a short illness on 2 February 1976. Although he retired from the Nottingham Eye Hospital in 1961, he had continued working as an ophthalmologist until just before his death. He was still a council member of the Ophthalmological Section of the Royal Society of Medicine and his cheerful and kindly presence was well known to members of the Midland and the North of England Ophthalmological Societies. He was President of the Midland Ophthalmological Society in 1951–52. For many years he was on the council of the Oxford Congress and served as Deputy Master of the Congress in 1960. He also took an active part in local medical affairs, having been secretary to the Nottingham Medico Chirurgical Society during the second world war and President in 1950. His career began in Edinburgh where he qualified in 1917 and he saw active service in the first world war as a Captain in the RAMC. Soon after the war he developed an enduring interest in his specialty and for nearly 47 years he practised in Nottingham. During this time he became greatly loved and respected and there are many who will miss his kindly attentions both as patients and colleagues.

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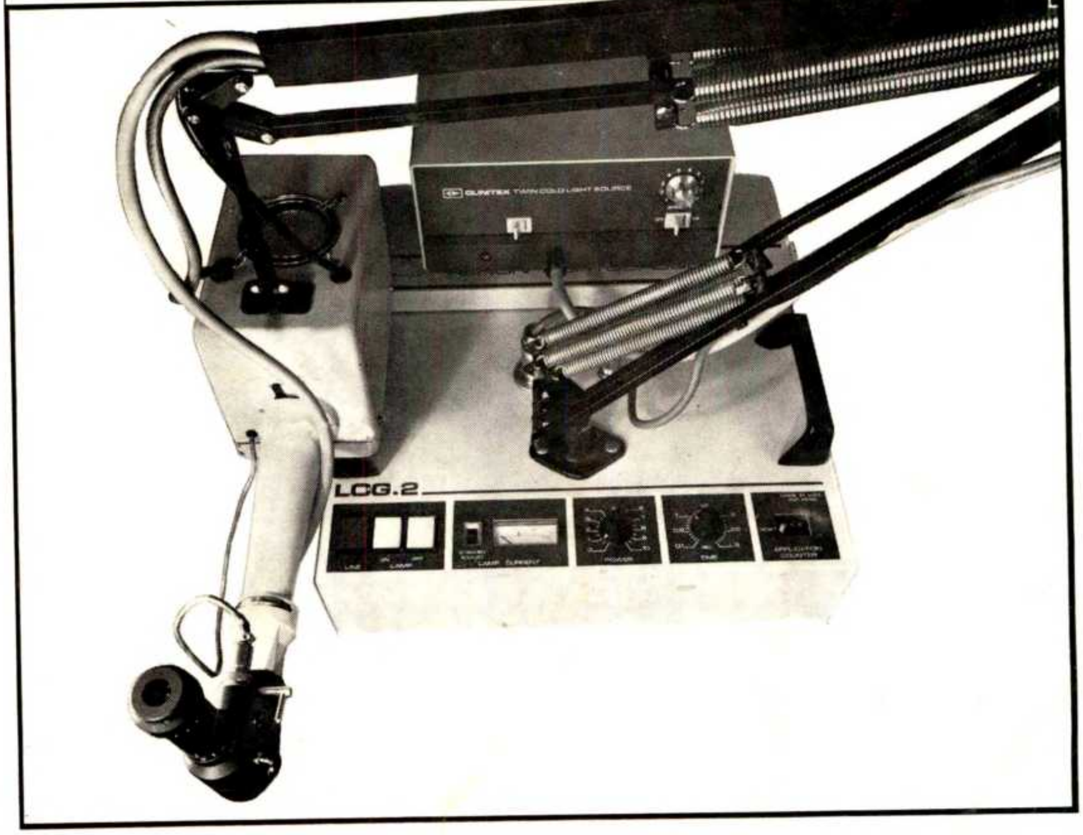

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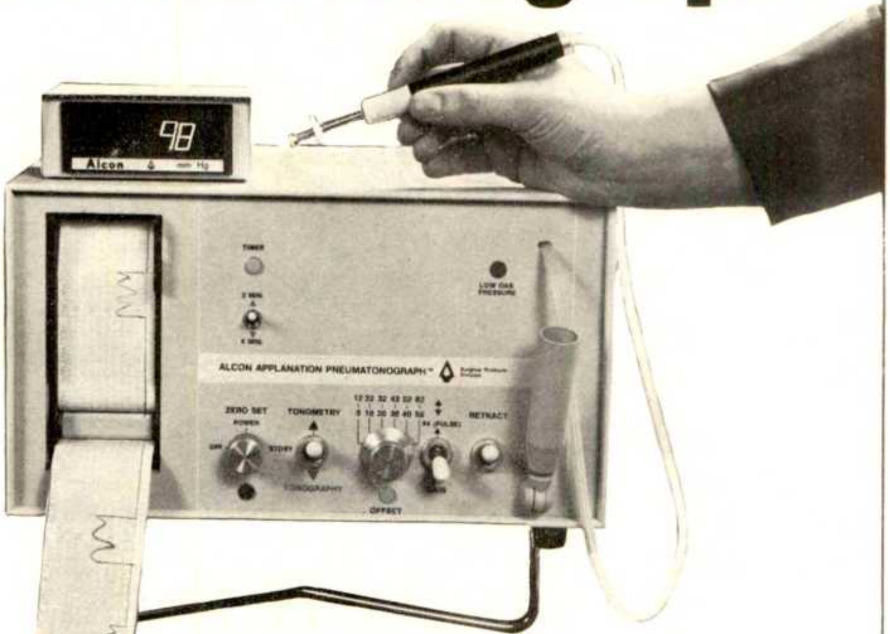

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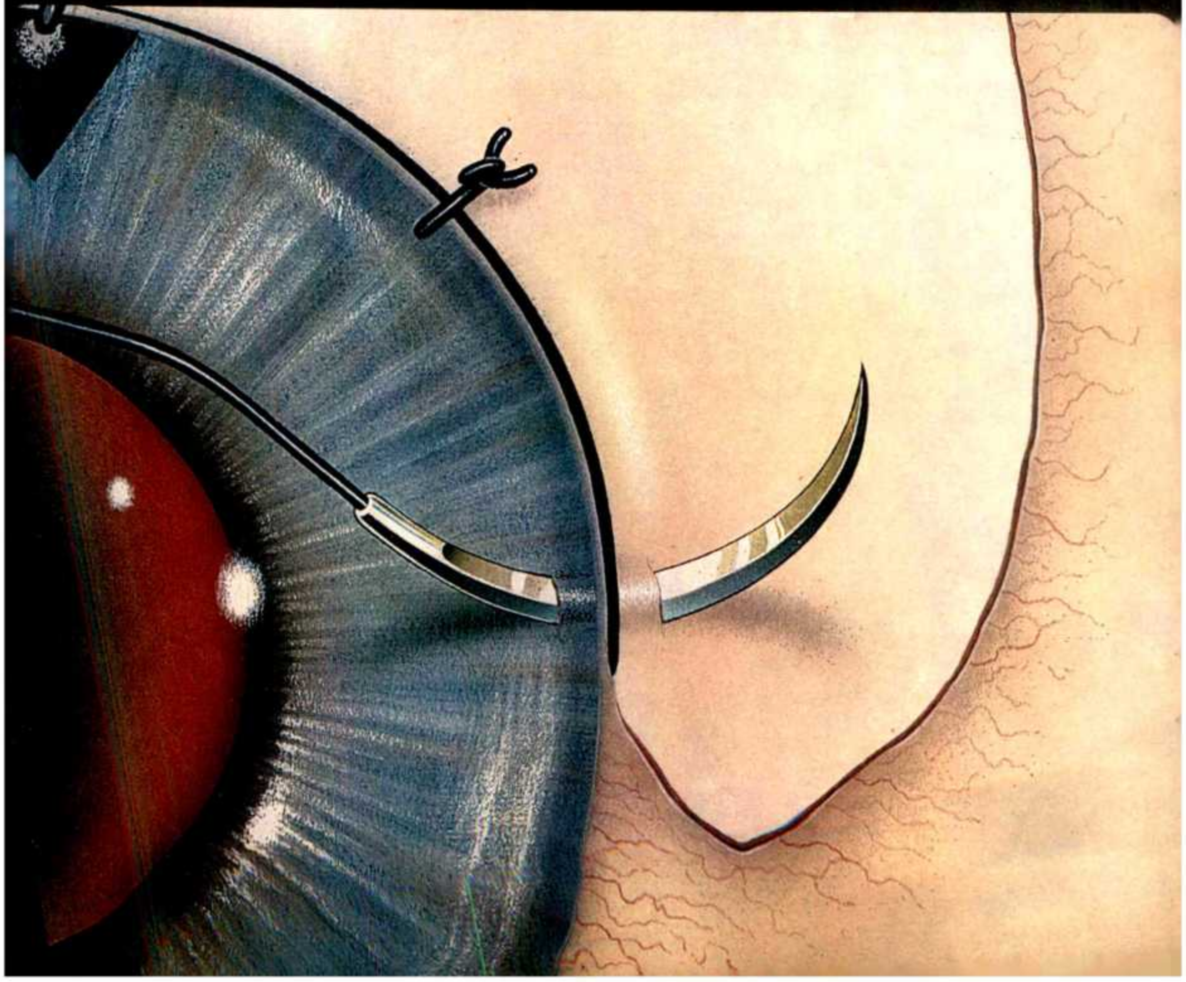

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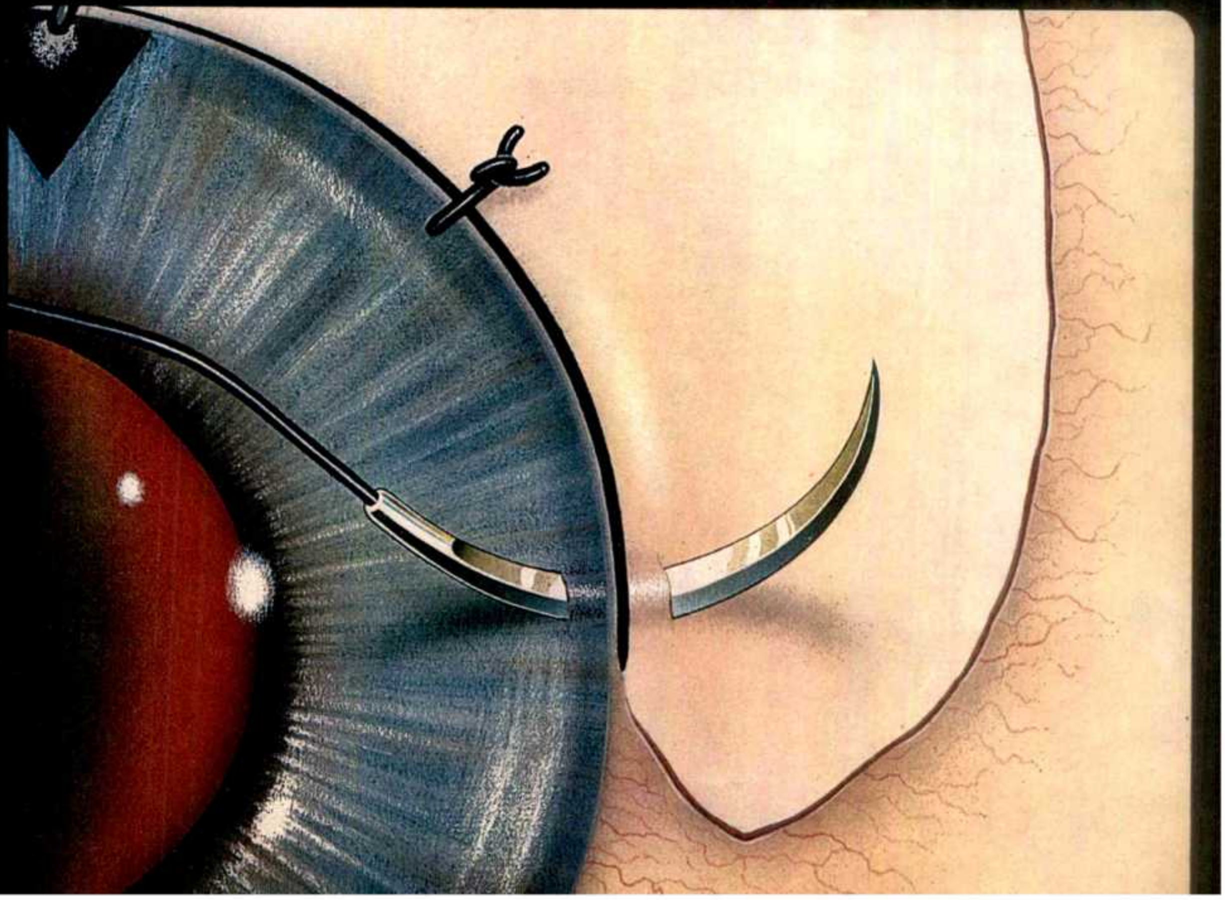

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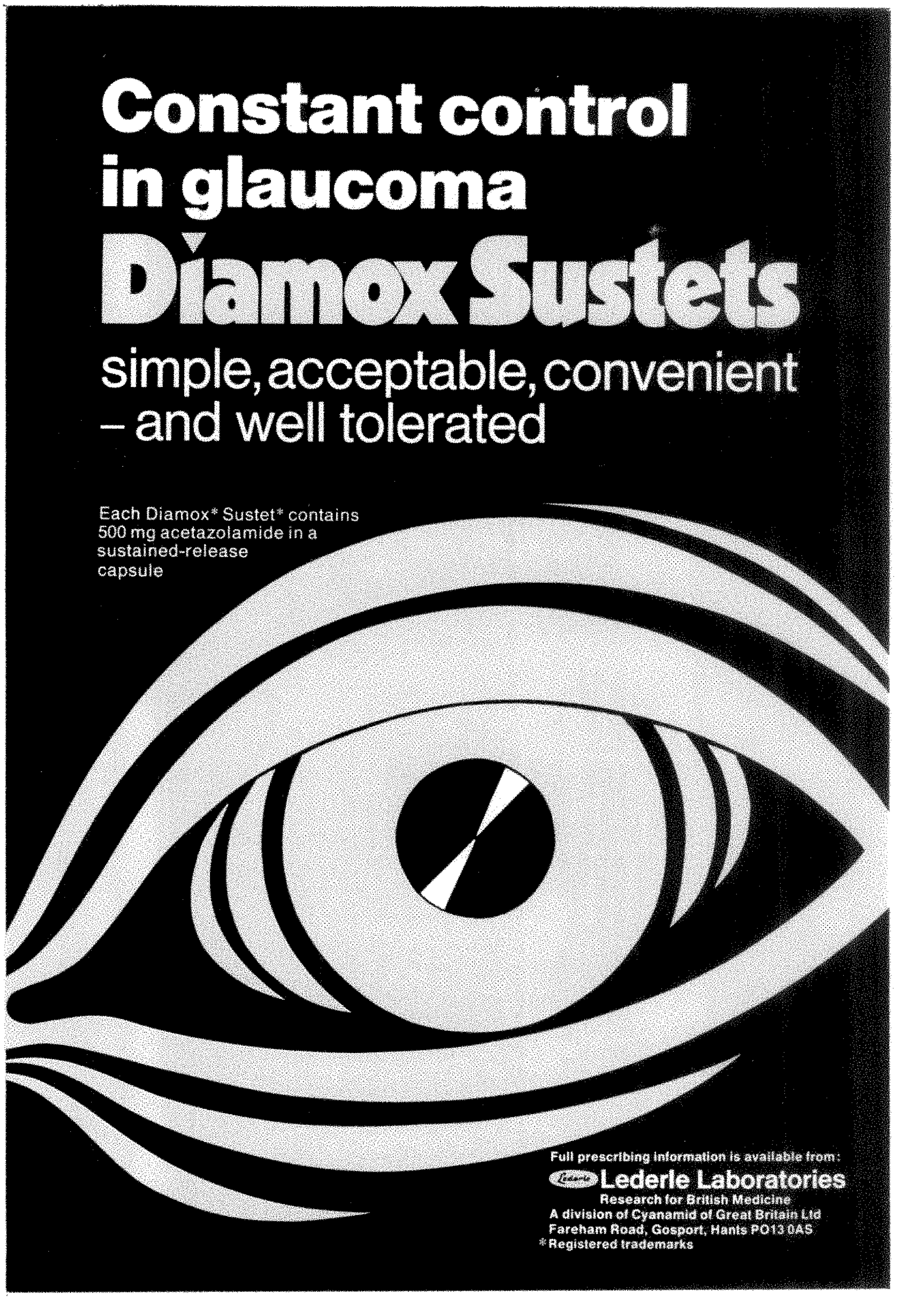

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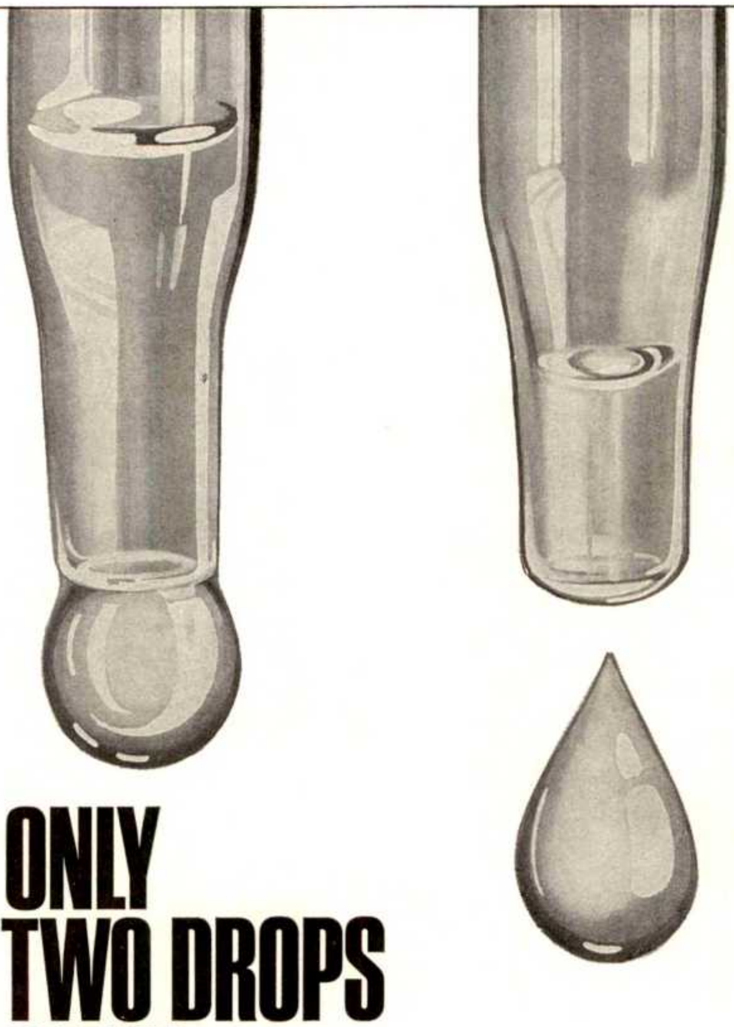

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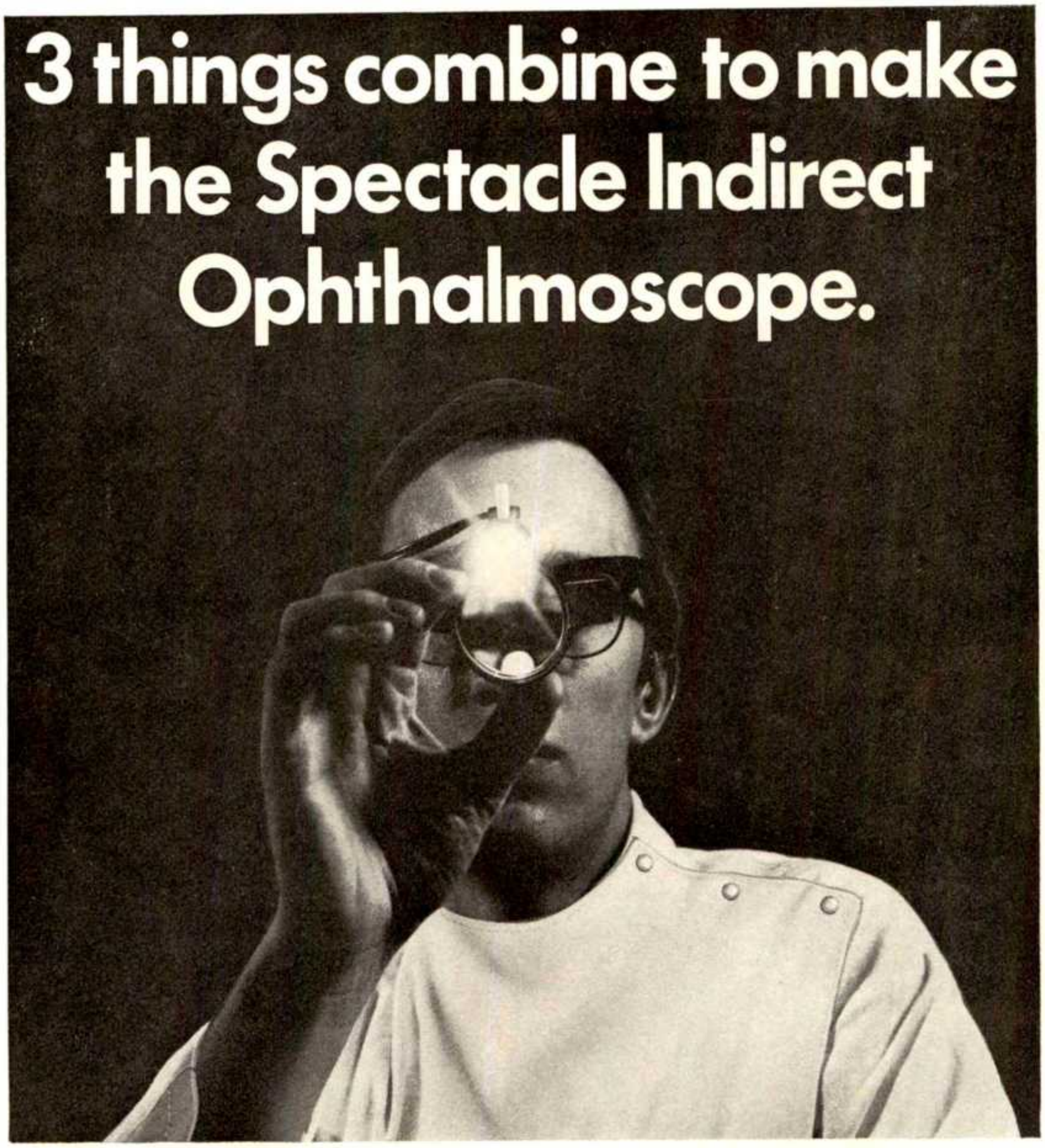
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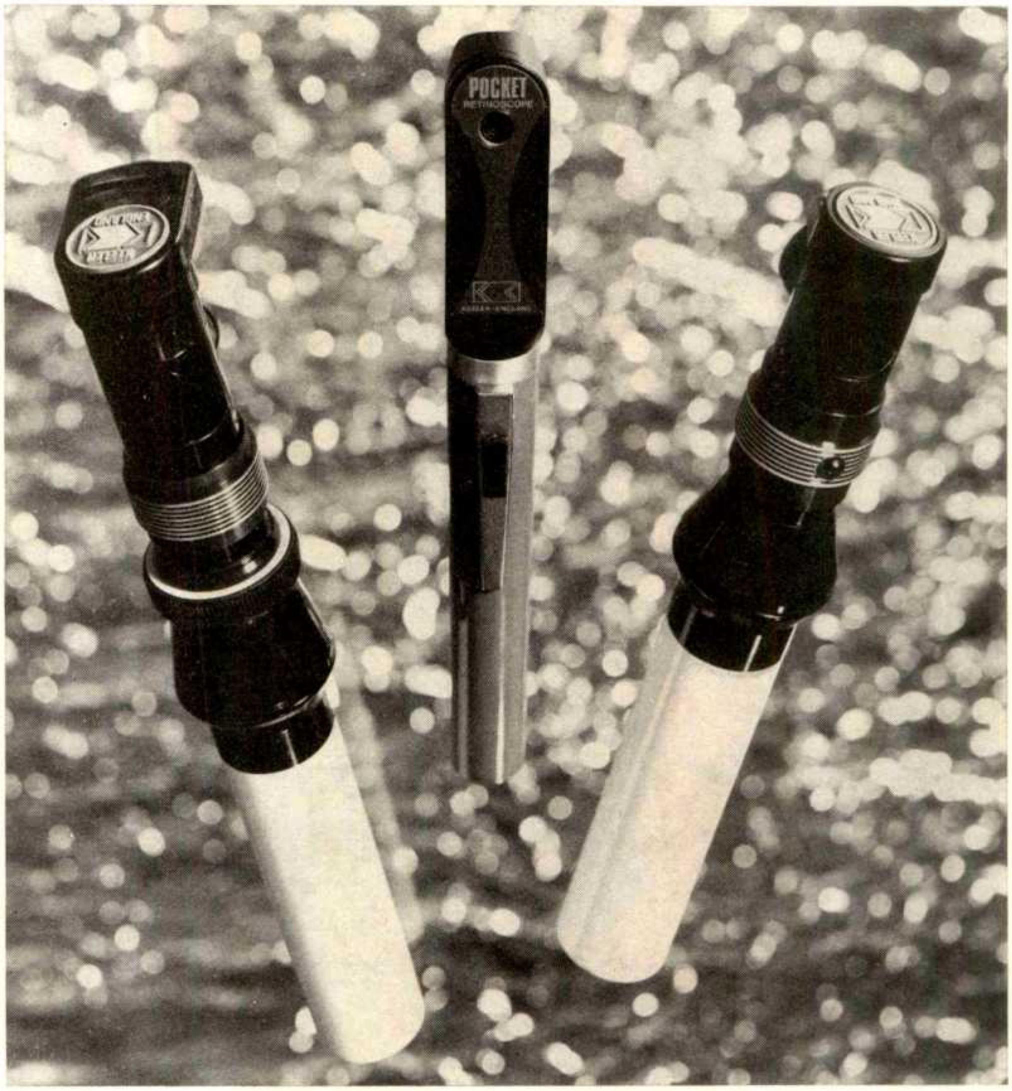

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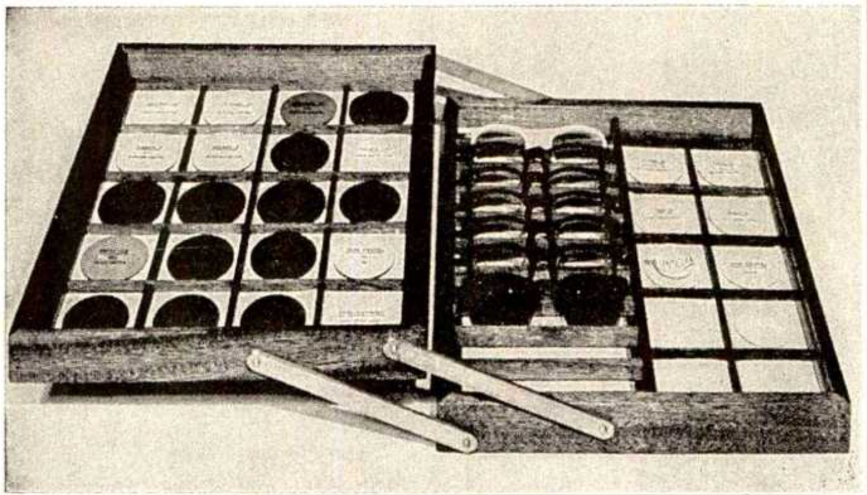

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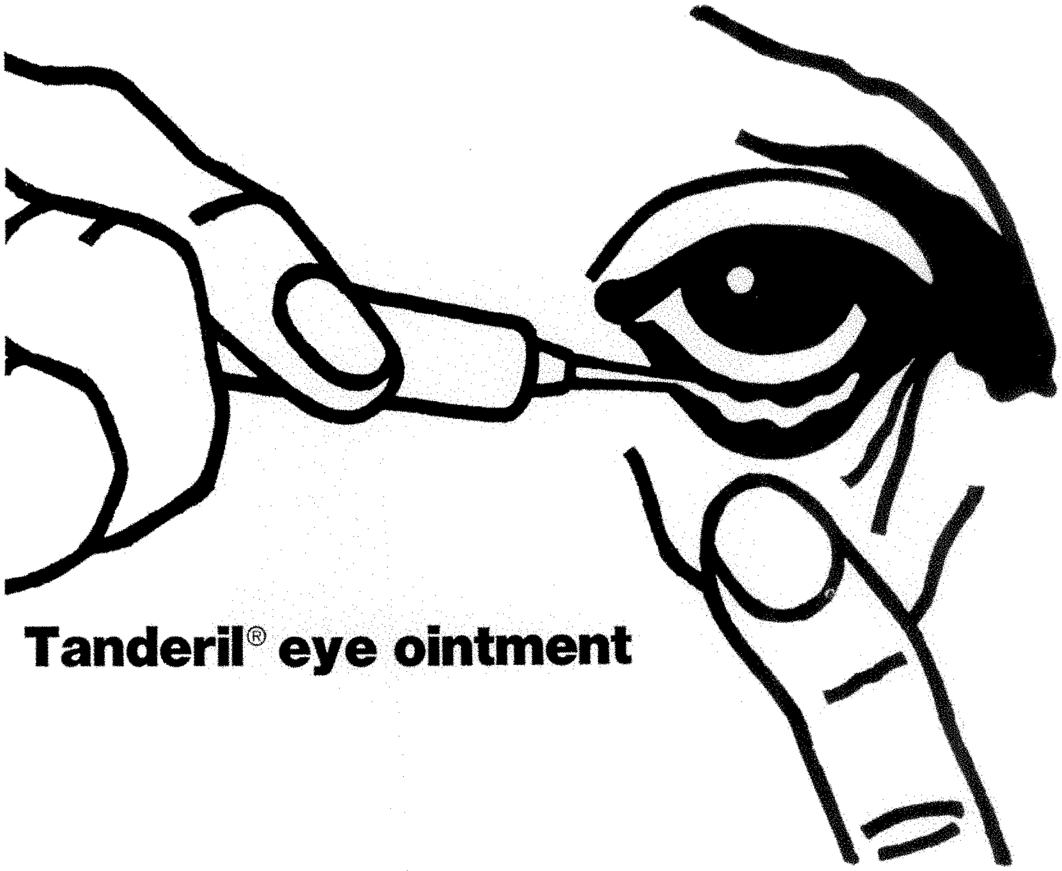

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Brit. J. Ophthal. (1976) **60,** 605

Editorial: Direct fungal infection of the eye and its prevention

The paper from Nigeria (page 607) makes a welcome and important contribution that expands our knowledge of the world-wide distribution and clinical importance of fungal infection of the eye (Gugnani, Talwar, Njoku-Obi, and Kodilinye, 1976). For some time it has seemed likely that loss of eyes from fungal infection in the humid tropical world is much more common than the literature would suggest (Jones, 1975a). Diagnostic facilities have seldom been available there, and in the absence of effective treatment there has been little point in pursuing the precise causation of such infections. A mycologically proved diagnosis was made in 21 out of 36 of the corneal ulcers presenting in the University of Nigeria Teaching Hospital at Enugu during a two-year period. Because of the selection of cases for study it is likely that many more fungal infections went unrecognized because they were not investigated. Most of these patients were agricultural workers and in many cases the infection followed trauma with palm tree or other vegetable material.

This report appears to be the result of the expansion of academic ophthalmology in the African continent rather than the result of a recent invasion of that region by *Fusarium solani*. It is likely therefore that it represents a first sampling of an important and widespread cause of loss of eyes in rural populations over a vast area in Central Africa. It is known that this is the case in the south eastern United States of America, India, and South East Asia and it will probably be shown to be so throughout Indonesia, New Guinea, the Pacific Islands, Northern Australia, tropical Central and South America, and the Caribbean area.

The predominant organism in the West African series was *F. solani* (12 out of 21 identified). The second most frequent was *Aspergillus fumigatus* and other *Aspergillus* species (five out of 21). In Europe, Britain, and the northern United States of America *A. fumigatus* and other *Aspergillus* species of environmental origin and *Candida albicans,* of which the reservoir is in humans, have been the commonest fungi responsible (Jones, Richards, and Morgan, 1969c).

Although *F. solani* has come to be recognized as an ocular pathogen only during the last 10 years, this finding has been reported extensively from the southern United States of America (Jones, Sexton, and Rebell, 1969d) and from a number of other countries including England (Jones, 1975a; Gugnani and others, 1976). Fusarium ulcers may present as superficial and rather unimpressive lesions, more often they progress rapidly to deep corneal disease or extensive corneal abscess formation, sometimes with scleral invasion (Jones, 1975a and b). As with other fungi there is a strong tendency for fungal invasion of the posterior chamber to lead to seclusion of the posterior chamber followed by forward displacement of the lens and iris from pressure of aqueous behind, with progressive shallowing of the anterior chamber giving rise to a malignant glaucoma that requires lens extraction with anterior vitrectomy and sometimes corneal transplantation (Jones, Jones, Lim, Bron, Morgan, and Clayton, 1969a; Jones, Jones, and Richards, 1969b; Jones 1975a and b). The most striking feature of ocular infections with *F. solani* is the speed and destructiveness with which they can develop. This commonly misleads the clinician to think that he is dealing with a bacterial infection.

The virulent pathogenic nature of ocular isolates of *F. solani* is clearly established: the ocular disease that occurs in man with infection by this organism has been reproduced in animals (Jones and others, 1969a). Furthermore, in all cases in which the biology of the ocular isolates has been reported, the organisms have grown especially well at 37°C and have had other biological differences from the more common isolates made from plant disease (Jones and others, 1969a; Jones, 1969d; Gugnani and others, 1976). This suggests that among the vast population of *F. solani* in the environment, much greater in the humid tropical areas than in the arid or cooler regions, there is an undetermined proportion of strains of *F. solani* that are especially well suited to invade the eye. Although many cases of infection by *F. solani* have followed trauma, some have had no history of injury (three out of 12 in the African report), nor have immunodeficiencies figured in the background of reported cases.

In 1962 John McLean said 'Our defences against fungi are indeed weak and clumsy'. The recent advances in chemotherapy of oculomycosis now mean that although few fungal infections of the eye are so trivial that they can be managed lightly, few are so severe that they should be despaired of, provided they can be treated at a centre with the required combination of skills. This has been brought about by the rational use of amphotericin B within its limited range of usefulness, the introduction of the wide spectrum polyene antifungal, natamycin, and the development of the imidazole antifungals: clotrimazole, miconazole, econazole, and thiabendazole, together with appropriate use of flucytosine for yeast-like fungi. These newer antifungals penetrate the eye well but are more selective in their action than the poorly penetrating but widely active natamycin (Jones, 1975a and b). Optimal antifungal treatment must therefore be guided by isolation and species identification of the infecting organism, with direct measurement of the antifungal sensitivities of the patient's own fungus.

The development of effective chemotherapy of fungal infection of the eye has a number of important implications. There is a strong case for the rapid referral of patients with oculomycosis for emergency management in a few centres especially equipped for and experienced in this work.

The second implication results from the frustrating delays that hold up the making available of a preparation or drug that is likely to be of use only for saving eyes infected with fungi: the forseeable therapeutic market may be unlikely to cover the costs of securing approval to market it in a variety of countries. If the compound is, like thiabendazole, already in widespread veterinary and agricultural use there may be further obstacles to its availability for treating oculomycosis. It is therefore desirable that national or international agencies should undertake or support the work to provide the data needed for approval to use and to market selected preparations.

The third implication is greatly accentuated by the report from West Africa. Topical antifungal chemotherapy of individuals at times of high risk should substantially reduce these potentially disastrous infections. These times are following ocular trauma, especially with plant or vegetable material. Fungal infection is only part of the overall problem of loss of eyes from suppurative keratitis, which should be amenable to a considerable measure of prevention. It should now be possible to produce a combined antifungal and antibacterial preparation for widespread and immediate prophylactic first aid use after trauma, especially in rural areas. Further surveys are needed however, to define the causes of suppurative keratitis leading to loss of eyes in various regions. These include Gram-positive and Gram-negative bacteria, a wide variety of ocular fungi especially *Fusarium* species and *Aspergillus* species and probably also some anaerobic bacteria. It will be of great interest to determine the world wide prevalence of ocular infection by *Acanthamoeba polyphaga, A. Castellani,* and other pathogenic freshwater amoebae, for these protozoa can cause suppurative corneal and intraocular infections resembling those due to fungi (Nagington, Watson, Playfair, McGill, Jones, and Steele, 1974; Watson, 1975; Nagington, 1975; Jones, McGill, and Steele, 1975; Ashton and Stamm, 1975; Jones, Visvesvara, and Robinson, 1975). These surveys require the provision and distribution of kits for diagnostic cultures and the provision of facilities for identification and the measurement of antimicrobial sensitivities. Local, national, regional, and international collaborations can contribute in this endeavour. Fortunately, the techniques required for bacteria, fungi, and the pathogenic freshwater amoebae are all simple and straightforward.

Further animal experimental work is needed to define optimal formulation of various antifungals and the effect of combinations of antifungals and antibacterials. But a likely combination to be used in an ointment might well be natamycin, polymyxin B, and an aminoglucoside such as gentamicin. Clotrimazole because of its wide spectrum of antifungal action, especially against *Aspergillus* species, and its good ocular penetration, would have a case for inclusion, as would econazole (Jones, 1975a and b).

In this Prevention of Blindness Year it would be appropriate for the World Health Organization to take the lead in catalysing the designation of a small number of institutions as reference centres for research in oculomycosis and related suppurative infections of the eye. This should boost and assist the collaborative endeavours that are essential in order to avoid the loss of eyes from suppurative infections.

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Brit. J. Ophthal. (1976) **60,** 607

Mycotic keratitis in Nigeria
A study of 21 cases

H. C. GUGNANI, R. S. TALWAR, A. N. U. NJOKU-OBI, AND
H. C. KODILINYE
From the Departments of Microbiology and Ophthalmology, University of Nigeria Teaching Hospital, Enugu, Nigeria

Mycotic keratitis is being increasingly recognized as an important problem in ophthalmic practice in several parts of the world (Emmons, Binford, and Utz, 1970). Reports on it from various countries have been comprehensively reviewed by DeVoe and Silva-Hutner (1972). Except for one record from Egypt of a corneal ulcer due to *Beauveria* sp. (Lichaa, 1933), information on the incidence and aetiology of mycotic keratitis in the African continent has been lacking. Therefore a report of 21 cases of this condition diagnosed during a period of two years at the University of Nigeria Teaching Hospital, Enugu, is of interest. This series of cases of fungal corneal ulcers, proved by culture, is one of the largest to be reported.

Materials and methods

The study was limited to cases in which the corneal ulcers were strongly suggestive of a fungal infection. Thirty-six such cases were investigated. A thorough clinical examination together with observation by slit lamp of the size, shape, position, and depth of the ulcer and the type of slough was undertaken, and satellite lesions on the cornea were looked for whenever possible. The patient's occupation, history of onset of the disease or injury, and previous treatment with corticosteroids or broad spectrum antibiotics were recorded. Scrapings for mycological investigation were taken from the edge or the base of the ulcers with a platinum loop under sterile conditions, taking as deep a scraping as possible. A portion of the scrapings was examined microscopically in 10 per cent potassium hydroxide and the remaining material cultured on slopes of freshly prepared Sabouraud's agar supplemented with chloramphenicol (0·05 mg/ml). Cultures were incubated at 28°C for 7 days and regularly examined. In cases in which microscopical examination of scrapings in KOH was negative and the culture was positive, or vice versa, more scrapings were collected and processed.

Results

Mycotic keratitis was diagnosed by the demonstration of fungal elements in corneal scrapings and positive cultures in 21 out of the 26 cases investigated. The salient clinical features and the infecting fungi in the 21 cases are shown in the Table. Twelve were caused by *Fusarium solani,* four by *Aspergillus fumigatus,* one by *A. flavus,* two by *Penicillium citrinum,* one by *P. expansum,* and one by an unidentified *Penicillium* sp.

Most of the cases were aged between 20 and 60 years. Eight of the 21 cases were women, and this possibly was because Nigerian women take an active part in outdoor and farm work. In 10 of the 15 patients with a history of trauma the injury was from vegetable matter—mainly palm tree, thorn or leaf—and in the remaining five from other causes.

The clinical features of the corneal ulcers were similar whatever the causative fungus. Most cases had a big central or paracentral ulcer with a dry slough at the base and raised edges. There was a greyish-white hypopyon in all cases except two which were seen at an early stage. Lack of vascularization was characteristic of these two cases. Satellite lesions were seen in one case, the causal agent being *F. solani.* In two cases, one due to *F. solani* and the other to *A. fumigatus,* the ulcer was in a very advanced stage of sloughing leading to panophthalmitis with no perception of light and faulty projection in all quadrants (Figs 1 and 2). Three cases due to *F. solani* had big central slough-

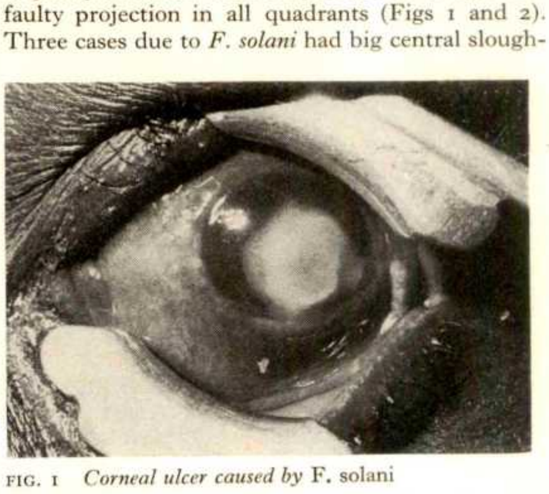

FIG. 1 *Corneal ulcer caused by* F. solani

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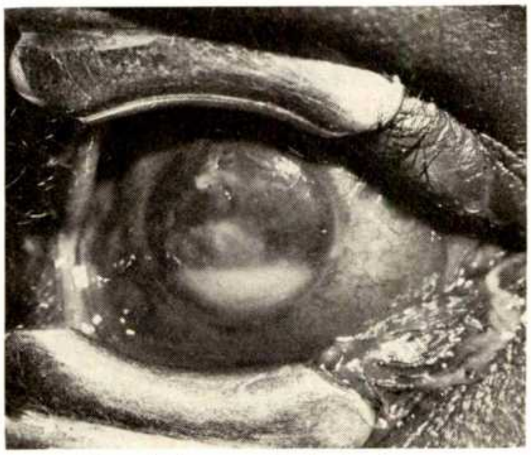

FIG. 2 *Corneal ulcer caused by* A. fumigatus

ing ulcers with hypopyon filling more than half of the anterior chamber; corneal abscess and endothelial plaque formation was observed in these cases. Fig. 3 illustrates the abundant hyphal elements of *F. solani* in the scrapings from a case of corneal ulcer. Histopathological studies of infected eyes in two cases of corneal ulcers in which the diagnosis was confirmed by culture showed invading hyphae of *A. fumigatus* in the corneal tissue (Fig. 4) and in the sclera. The tissue reaction in these cases manifested as necrosis accompanied by acute inflammatory cellular infiltration. The main morphological features of representative isolates of *F. solani*, *A. fumigatus*, and *P. citrinum* are shown in Figs 5 to 8. All the 12 isolates of *F. solani* grew well at 37°C and survived at 40°C for more than three weeks.

Treatment with amphotericin B eye drops was tried along with the routine supportive treatment of ulcers and hypopyon in six cases, four of which were caused by *F. solani* and two by *A. fumigatus*. The response was satisfactory in three cases, in which the ulcer healed and left a leucomatous corneal opacity. In some other cases repeated cauterization with pure carbolic acid was tried but it helped only to salvage the eye for cosmetic reasons. Evisceration had to be done in three cases in which the hypopyon had organized causing an endothelial plaque and leucoma formation. In one case, due to *F. solani*, in which hypopyon could not be reduced, paracentesis was tried without any significant improvement. However, it helped to confirm the diagnosis as the material collected showed fungal hyphae on direct microscopical examination and *F. solani* was recovered in culture.

Table *Salient clinical features and causative fungus in* 21 *cases of myotic keratitis*

Case no.	*Age (years)*	*Sex*	*Occupation*	*Eye affected*	*History of trauma*	*Previous treatment*	*Causative fungus*
1	70	Male	Farming	Left	Palm tree thorn	Natural medicine	*Aspergillus fumigatus*
2	50	Female	Farming	Right	—	—	*Fusarium solani*
3	24	Male	Fitter	Left	Mechanical tool	Corticosteroids	*F. solani*
4	22	Female	Farming	Right	Palm kernel	—	*F. solani*
5	22	Female	Housewife/farming	Left	Palm kernel	—	*F. solani*
6	35	Male	Farming	Right	Dust particles	—	*F. solani*
7	45	Male	Farming	Left	Palm tree thorn	—	*A. fumigatus*
8	18	Female	Student	Right	Hit by stone	—	*F. solani*
9	40	Male	Farming	Right	Palm tree thorn	—	*Penicillium* sp
10	30	Female	Farming	Left	—	—	*A. fumigatus*
11	35	Male	Farming	Left	—	—	*F. solani*
12	54	Male	Farming	Right	Bush plant injury	Corticosteroids	*P. citrinum*
13	44	Male	Colliery worker/farmer	Left	Palm tree thorn	—	*F. solani*
14	44	Female	Housewife	Right	—	—	*P. citrinum*
15	60	Female	Housewife	Right	—	—	*A. flavus*
16	51	Male	Farming	Left	Hit by stone	—	*F. solani*
17	45	Male	Farming	Right	Stick injury	Self medication with eye drops	*F. solani*
18	16	Female	Student	Left	Hot-oil burn	—	*P. expansum*
19	16	Male	Student	Right	—	—	*F. solani*
20	44	Male	Student	Left	Stick injury	Self medication with ointment	*A. fumigatus*
21	33	Male	Farming	Left	Cashewnut tree branch	—	*F. solani*

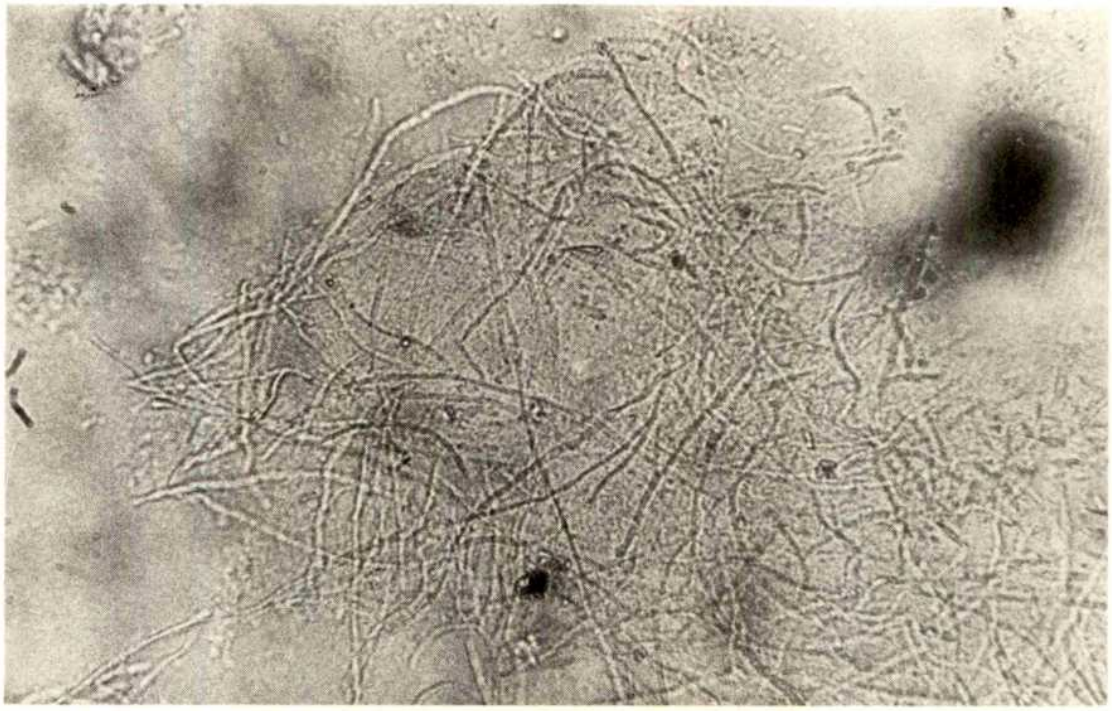

FIG. 3 *Hyphae of* F. solani *in corneal scraping. KOH preparation.* ×460

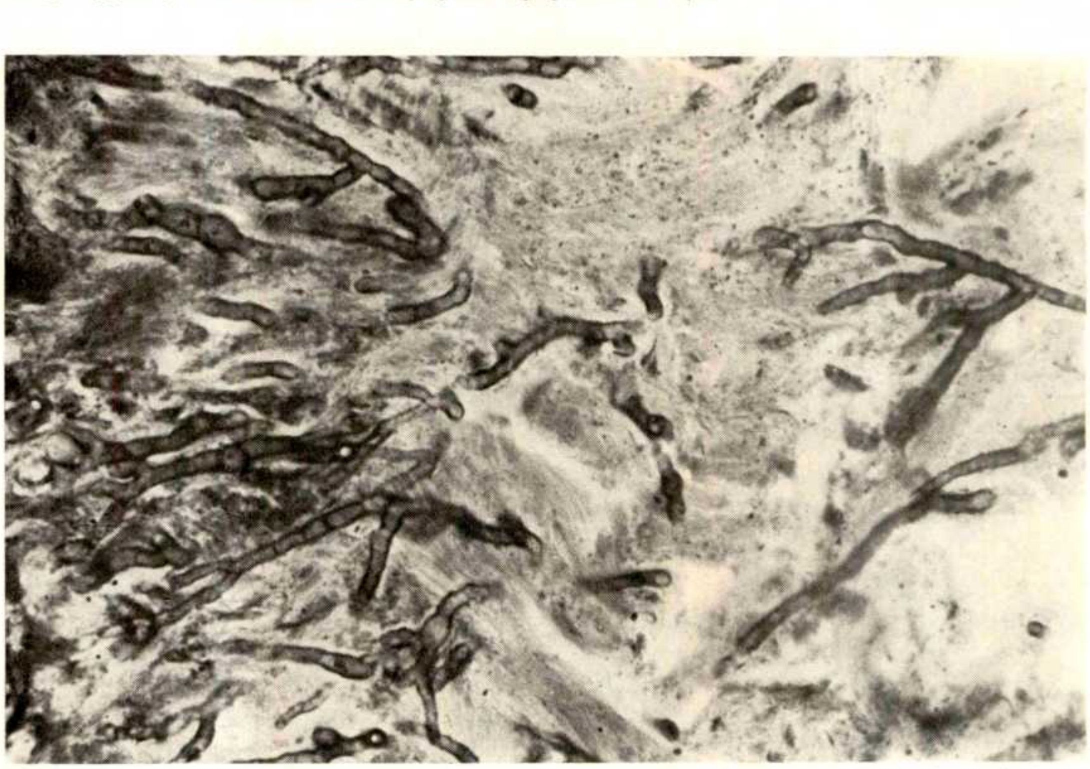

FIG. 4 *Histological section showing septate, dichotomously branching hyphae characteristic of* A. fumigatus *in the corneal tissue. Haematoxylin and eosin.* ×410

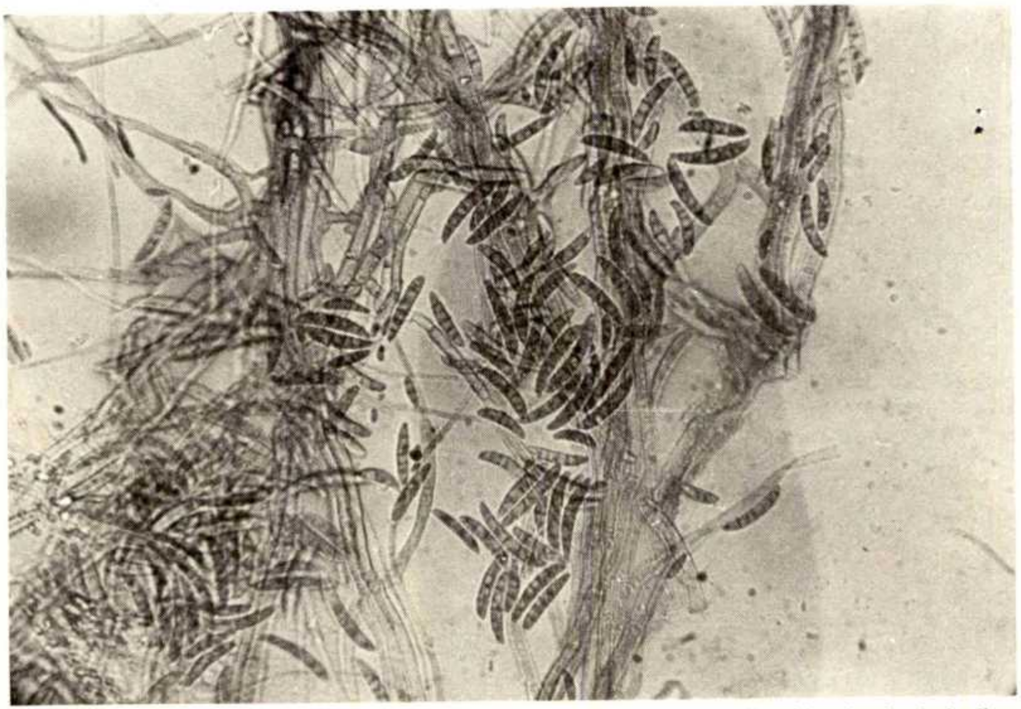

FIG. 5 F. solani *in culture showing clusters of inequilaterally fusoid macroconidia with pointed apical cells. Lactophenol blue mount.* ×375

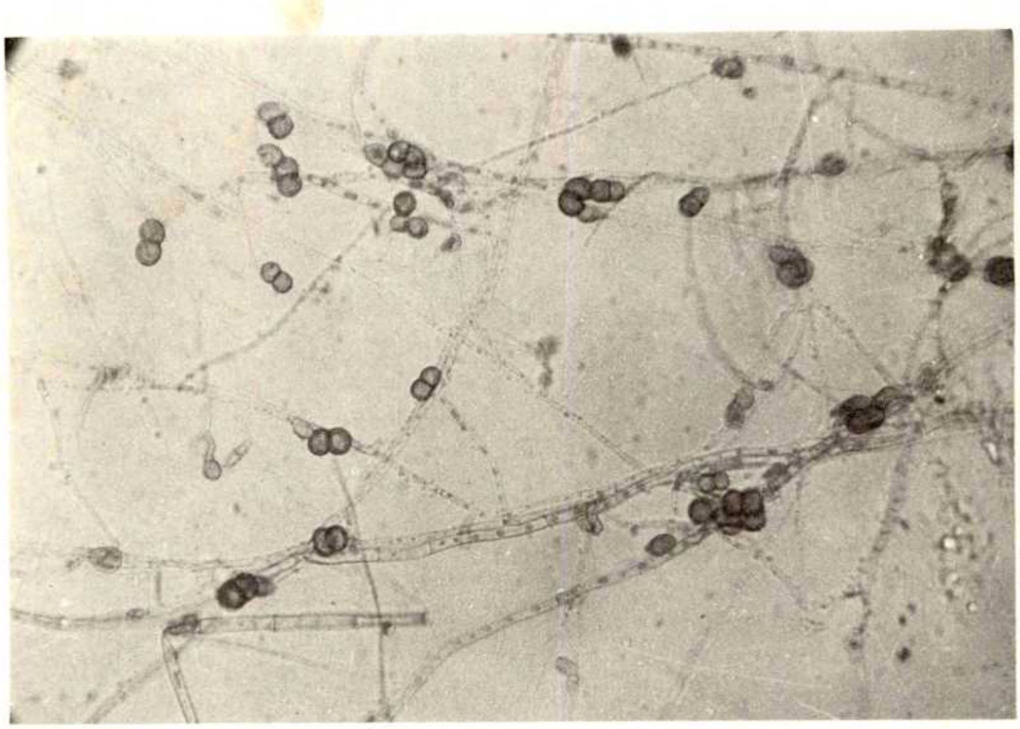

FIG. 6 F. solani *in culture showing abundant terminal and intercalary, subglobose, smooth to slightly rough-walled chlamydospores. Lactophenol blue mount.* ×375

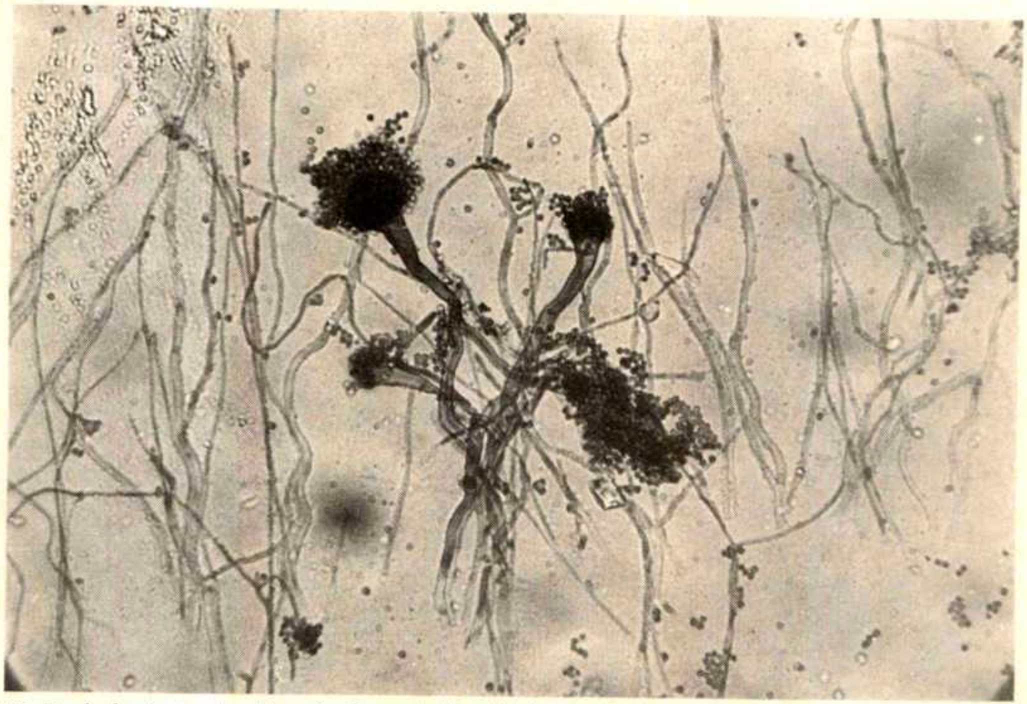

FIG. 7 A. fumigatus *in culture showing typical conidiophores with clavate vesicles and uniseriate sterigmata (phialides) bearing chains of conidia. Lactophenol blue mount.* ×375

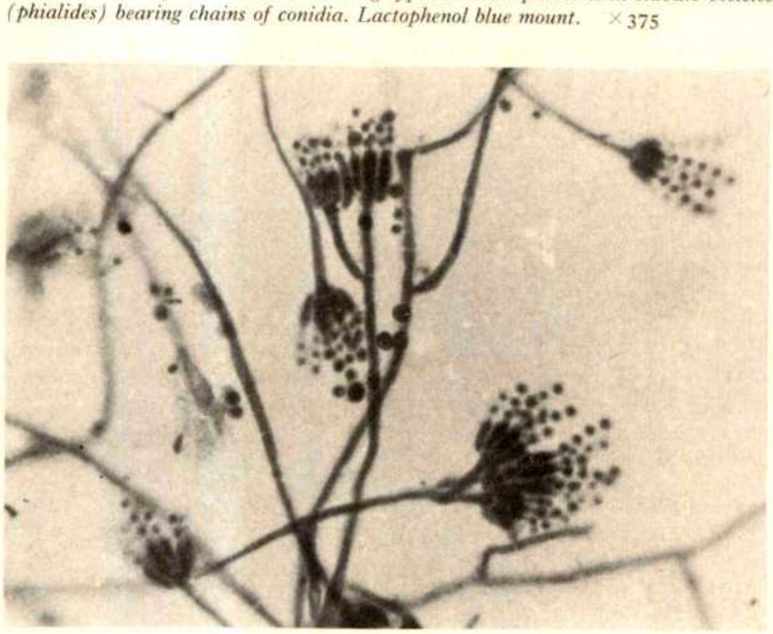

FIG. 8 Penicillium citrinum *in culture showing monoverticillate heads of conidia occurring singly and in bunches. Lactophenol blue mount.* ×375

Enucleation was done in another two cases in which the whole of the anterior segment was involved and there was no perception of light or projection. It was in these two cases that histological examination showed the presence of hyphae of *A. fumigatus* in the corneal tissue and in the sclera. Therapeutic keratoplasty could not be undertaken owing to lack of facilities. The new drug natamycin (Pimaricin), reported to be successful in treatment of *F. solani* keratitis (Jones, Forster, and Rebell, 1972), was not locally available. However, with a small quantity of the pure antibiotic kindly supplied to us by Gist-Brocades, Research and Development Division, Delft, Holland, we have tested the *in vitro* sensitivity of eight isolates of *F. solani* from our cases by the tube dilution method in Sabouraud's dextrose broth. These isolates were found to be sensitive to the antibiotic at a concentration of 5 to 10 μg/ml.

Discussion

This is the first report of cases of mycotic keratitis from Nigeria or West Africa. The actual incidence of mycotic keratitis may be much higher since, owing to pressure of work, we could not investigate several other suspected cases among the large number of patients with corneal ulcers attending our clinic. The incidence of cases by age and sex is similar to that reported by Sood, Ratnaraj, Balaraman, and Madhavan (1968).

Previous corneal trauma and topical application of corticosteroids or broad spectrum antibiotics, or both, have been significantly associated with mycotic keratitis in man. (Chick and Conant, 1962; Zimmerman, 1963; DeVoe and Silva-Hutner, 1972). Although only 15 out of our 21 patients gave a history of trauma, probably the remaining six had also sustained some mild injury which went unnoticed at the time. Notably, most of our patients were farmers and trauma was most often from palm tree leaf, thorn, kernel, or other plant objects. Most Nigerians work in agriculture and are therefore more prone to outdoor trauma. Reddy, Satyendran, Satapathy, Kumar, and Reddy (1972) and Dasgupta, Gupta, Ray, Sunderaraj, Ramamurthy, and Lamba (1973), in their reports on keratomycosis in India, have also mentioned that most of their patients were agricultural workers with a history of trauma sustained while working in the fields.

Only a few of our patients gave a definite history of topical application of corticosteroids. However, probably in a few other cases the unknown drops or ointment used in earlier self-medication may have been preparations of corticosteroids or broad spectrum antibiotics since both these are easily available in local markets without prescriptions.

A wide range of fungi are known to cause mycotic keratitis and the predominant aetiological agents vary in different geographical areas (DeVoe and Silva-Hutner, 1972). The 21 isolates of fungi from corneal ulcers in our series represented three different genera—that is, *Fusarium, Aspergillus,* and *Penicillium*—*F. solani* being the predominant aetiological agent represented by 12 isolates. In an earlier study of 38 cases of fungal corneal ulcers from Florida, USA (Jones, Sexton, and Rebell, 1969), 29 were proved to be caused by *Fusarium* sp., the commonest being *F. solani,* represented by 11 isolates. A few cases of *F. solani* keratitis have also been reported from other areas in the USA (Halde and Okumoto, 1966), Argentina (Zapater and Arrechea, 1975), Venezuela (Cordero-Moreno, 1973), Colombia (Greer, Brahim, and Gonzalez, 1973), Ceylon (Nityananda, Sivasubramaniam, and Ajello, 1962), Japan (Matsumoto, 1972; Suga, 1972), and Singapore (Jones, Jones, Lim, Bron, Morgan, and Clayton, 1969).

F. solani is a saprophyte of world-wide distribution and a well-known plant pathogen affecting a host of economically important plants (Booth, 1971). Although we could not procure *F. solani* isolates of plant origin for a comparative study, the ability of our clinical isolates of the fungus to grow well at 37°C and survive at 40°C for more than three weeks confirms the observation made by Jones and others (1969). As suggested earlier (Emmons and others, 1970), strains of *F. solani* which cause human disease have possibly a tropical or subtropical distribution.

Summary

A clinical and mycological study of 21 cases of mycotic keratitis, a clinical entity not yet reported from Nigeria or West Africa, showed that *Fusarium solani* was the predominant aetiological agent. It was isolated from 12 cases. Four of the remaining nine cases were caused by *Aspergillus fumigatus,* one by *A. flavus,* two by *Penicillium citrinum,* and one each by *P. expansum* and *Penicillium* sp. All the 12 isolates of *F. solani* grew well at 37°C and survived at 40°C. Two cases, one due to *F. solani* and the other to *A. fumigatus,* were accompanied by panophthalmitis.

We thank Mr A. J. Brooks, head of the Medical Illustration Unit, for the clinical photographs and Dr A. V. Suseelan, Department of Morbid Anatomy, for the histological preparations. We also thank the University Senate Research Grant Committee for financial support for the study and Dr C. Booth, of CMI Kew, Surrey, for identifying some of our isolates of *F. solani.*

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Unsuspected fungal endophthalmitis diagnosed in vitrectomy specimen

BARBARA PERINA, GEORGE H. KURZ, AND RAINER N. MITTL
From the Department of Ophthalmology, New York University Medical Center

Mycotic infections of the eye, as in other areas of the body, have been increasing. Nearly 100 different fungal species have been reported in ocular infection (Jones, 1975). This trend has been attributed to many factors including the use of corticosteroids and antibiotics and also to conditions causing decreased host resistance (Anderson, Roberts, Gonzalez, and Chick, 1959; Veirs and Davis, 1958; Rheins, Suie, Van Winkle, and Havener, 1966; Ley and Sanders, 1956; François and Rysselaere, 1972; Wolter, 1962).

The observation of multiple septate hyphae in the microscopical examination of a vitrectomy specimen from a patient in whom endophthalmitis was not suspected before surgery prompted the present report. To our knowledge this is the first account of mycotic endophthalmitis diagnosed from material obtained by vitrectomy.

Report of a case

A 47-year-old White man with diabetes mellitus and mild congestive heart failure had an ocular history which included advanced diabetic retinopathy, recent vitreous haemorrhage, and neovascular glaucoma. The glaucoma was controlled medically and with penetrating cyclodiathermy of the left eye in November 1972. A mild anterior segment reaction followed this procedure and was treated intermittently with topical corticosteroids until January 1974.

On examination in January 1974, the vision was right eye: hand movements, and left eye: perception of light with projection. The right eye had rubeosis iridis and proliferative diabetic retinopathy. In the left eye there were minor areas of rubeosis, cataractous changes of the lens, and a dense vitreous haemorrhage. The fundus could not be seen. Ultrasound study of the left eye revealed relatively dense opacities and membranes within the vitreous. Vitrectomy was suggested for the left eye and performed in July 1974, using the roto-extractor (Douvas, 1975).

During the procedure a peculiar dense-white rubbery substance was encountered in multiple areas of the vitreous cavity. Some of this material was submitted to the pathology laboratory. Microscopical examination revealed patches of proteinaceous exudate with large numbers of closely packed septate fungal hyphae (Figs 1 and 2). A few mycotic granules were observed (Figs 1 and 3). These were considered suggestive, but not diagnostic of coccidioidomycosis. Scattered lymphocytes were noted in some areas in association with the hyphae (Figs 2 and 4). Cultures for fungi were not done.

After this unexpected finding, the patient was put in hospital for a complete medical examination. He denied having any systemic symptoms, and his diabetes and congestive failure were well under control. He denied past or present ocular pain and the general physical examination was unremarkable except for moderate obesity. On examination of the eyes the vision was right eye: perception of light; left eye: no perception of light. Intraocular pressure was right eye 16 and left eye zero by applanation. The right eye had otherwise remained essentially unchanged since January 1974. In the left eye the lids and adnexa were normal. There was marked injection of the conjunctiva, mild microcystic oedema of the cornea, and an organizing haemorrhage involving approximately 90 per cent of the anterior chamber. These findings had been present since the vitrectomy. The blood in the anterior chamber prevented further examination of the eye.

In an attempt to find a possible source of the fungal infection, extensive laboratory studies were done in addition to the medical examination. Complete blood count, urine analysis, and blood cultures were negative. Serum profile was normal except for a raised level of glucose. Conjunctival cultures were negative for fungi. Anterior chamber and vitreous taps were not done. Skin tests for histoplasmosis and coccidioidomycosis were negative. Chest, skull, and sinus *x*-rays showed no abnormalities. A liver scan revealed an enlarged spleen for which no explanation was found. Microscopical slides from the vitrectomy were reviewed by several mycologists, but the species of fungus could not be positively identified.

During the patient's stay in hospital no evidence of fungal infection could be found elsewhere in the body and two years later he was healthy without systemic complaints. The left eye was phthisical. A follow-up medical examination failed to reveal any coccidioidal lesions.

The patient's record for the two years before the vitrectomy showed no sign of endophthalmitis, although he had been examined by numerous ophthalmologists during the period. An infection of the external ocular structures, specifically corneal ulcer, was never present. There was no history of accidental trauma. The cyclodiathermy, which was followed by a mild anterior segment

Address for reprints: Barbara Perina, MD, Department of Ophthalmology, New York University—Bellevue Medical Center, New York, New York 10016, USA

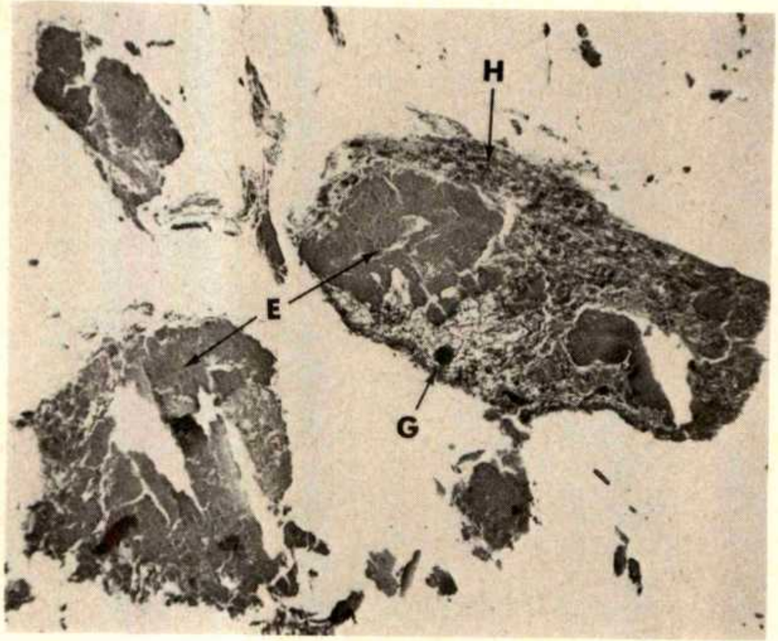

FIG. 1 *Matted hyphae (H), surrounding patches of proteinaceous exudate (E). Mycotic granule (G). Haematoxylin and eosin.* ×35

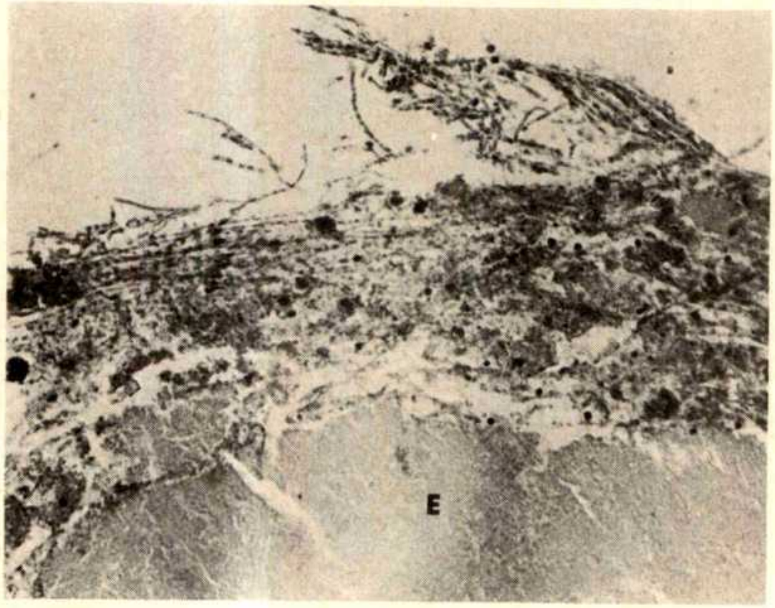

FIG. 2 *Densely packed septate hyphae with scattered lymphocytes Exudate (E). Haematoxylin and eosin.* ×224

reaction, preceded the vitrectomy by 20 months. Fungal endophthalmitis after cyclodiathermy has not been reported to our knowledge. We believe it unlikely, although not inconceivable, that the fungi gained entrance to the eye at the time of the cyclodiathermy in this case.

Discussion

The hyphae encountered in the microscopical sections are believed to reflect the true disease rather than a contaminant for the following reasons: their presence on all slides of this case; their intimate association with the eosinophilic exudate; their large number; absence of fungal contamination of other cases concurrently processed in the laboratory; the presence of mycotic granules; the presence of lymphocytes, and the unusual density and difficulty cutting the membranes encountered

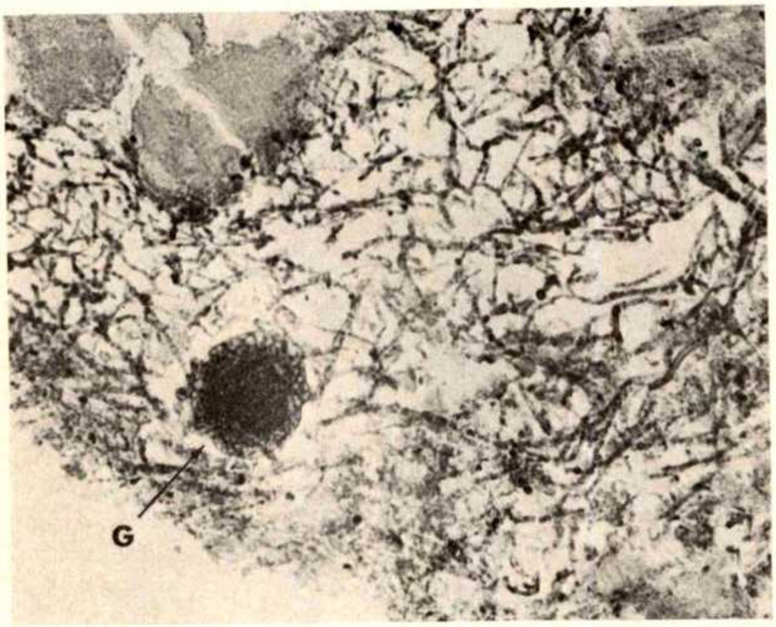

FIG. 3 *Mycotic granule (G) amid multiple septate hyphae. Haematoxylin and eosin.* ×224

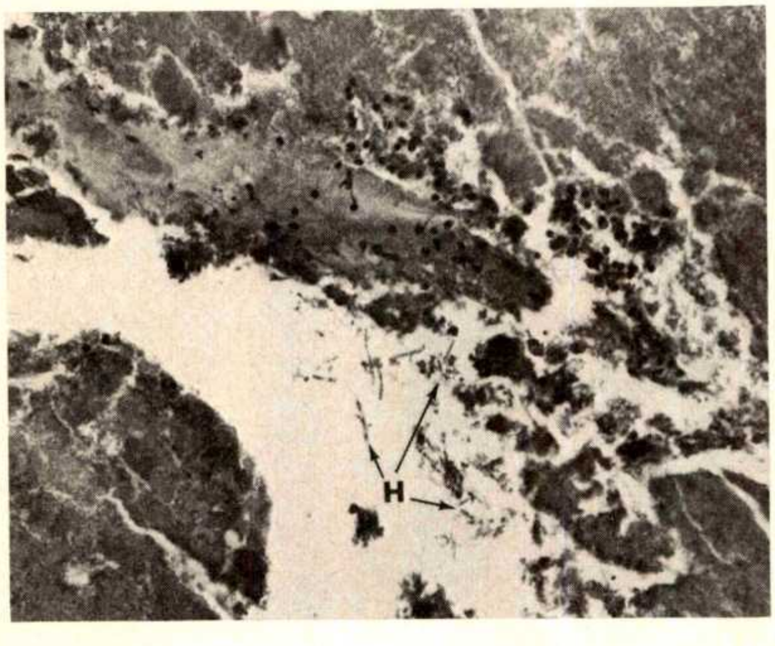

FIG. 4 *Scattered lymphocytes in proteinaceous exudate. Small number of hyphae (H). Haematoxylin and eosin.* ×224

during surgery, making the procedure much longer than anticipated.

Intraocular infections caused by fungus (McClean, 1963) may result from:

1. Direct invasion of the external ocular structures with resulting fungal conjunctivitis, fungal keratitis, and fungi in the lacrimal passages. Infection may then spread to deeper tissues.
2. Extension from neighbouring areas, such as the skin of the face, nasopharynx or sinus, extending into the orbit.
3. Exogenous route: or direct introduction intraocularly, either traumatic or surgical, most commonly after cataract surgery.
4. Endogenous route: or haematogenous route. This may be considered in cases in which there is no infection of the cornea or adnexa

and there is no history of ocular surgery or trauma. It may be subdivided into two types:

A. Ocular involvement with an overt source.

B. Ocular involvement with an occult source.

Oculomycosis, as a complication of intraocular surgery (Theodore, Littman, and Almeda, 1961; 1962) and traumatic injury (Fine and Zimmerman, 1959), is being recognized with increasing frequency. Endogenous endophthalmitis is less frequently recognized (Bonatti, Jaeger, and Frayer, 1963; Harley and Mishler, 1959). Our case appears to fall into the last category: endogenous intraocular infection without apparent systemic involvement.

Intraocular infections caused by coccidioidomycoses have been reported as cases of uveitis and chorioretinitis (François and Rysselaere, 1972). In 1958, a case was presented of a patient with generalized coccidioidomycosis with a granulomatous uveitis (Brown, Kellenberger, and Hudson, 1958). Histopathological examination revealed granulomatous inflammatory nodules in the iris and ciliary body. These nodules contained giant cells with spherules, surrounded by an infiltrate of lymphocytes, plasma cells, and epithelioid cells. Another interesting case of iridocyclitis with iris nodules was reported in 1967 (Pettit, Learn, and Foos, 1967). Cultures of aqueous grew *Coccidioides immitis*. Of note in this case is that there was no evidence of disseminated coccidioidomycosis.

Iris nodules were not noted clinically in our patient before the vitrectomy. After that procedure the patient had almost a total hyphaema, and the iris could not be visualized.

Endogenous intraocular infection due to fungi was considered very rare 15 to 20 years ago. Harley and Mishler (1959) pointed out that only 14 such cases had been reported in the literature and added one case of their own. Fungi were grown from a systemic site in only one of these cases. In more recent years these infections are being reported more frequently. Freeman, Davis, and Maclean (1974) reviewed the literature on *Candida* endophthalmitis. There were 49 cases and all were reported during the 10-year period 1962–72. Systemic involvement was found in 14 patients and was questionable in 5; 30 had no evidence of systemic fungal involvement. Ocular symptoms were present in most of the cases. Naidoff and Green (1975) reviewed the literature on 17 patients reported with endogenous *Aspergillus* endophthalmitis. Fourteen of 16 on whom this information was available had some underlying predisposing disease. Ocular symptoms were present in most of the patients.

The most common cause of endogenous fungal endophthalmitis today are the *Candida* species, followed by the genus *Aspergillus*. Some patients with infections secondary to *Candida*, *Aspergillus*, or other mycotic organisms do not have rapidly fatal diseases and may even be asymptomatic. As pointed out recently in the literature, some of the earlier reported cases in which no systemic source was identified, as well as our present case, undoubtedly fit into this category.

Summary

A vitrectomy specimen obtained with the roto-extractor from a diabetic patient with vitreous haemorrhage revealed fungal endophthalmitis on microscopical examination. Endophthalmitis was not suspected before the procedure. Extensive medical examinations failed to reveal any evidence of systemic fungal disease. The case exemplifies endogenous mycotic endophthalmitis of occult origin, the first of its kind, we believe, to be diagnosed in this manner.

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Encephalitozoonosis (nosematosis) causing bilateral cataract in a rabbit

NORMAN ASHTON, CHARLES COOK, AND FRANCIS CLEGG
From the Department of Pathology, Institute of Ophthalmology, University of London, and Ministry of Agriculture, Fisheries and Food, Loughborough, Leicestershire

Encephalitozoonosis, first described by Wright and Craighead (1922), is a chronic disease of rodents being a common and usually latent condition in many colonies of rabbits with a prevalence of 15 to 76 per cent (Pakes, 1974); it has been reported in a wild rabbit. It is caused by a microsporidan parasite *Encephalitozoon cuniculi*, the name given by Levaditi, Nicolau, and Schoen (1923). References to its identification, taxonomy, and pathology are to be found in the reviews of Petri (1969) and Pakes (1974). This parasite has also been described in blue foxes (Kangas, 1971; Kull, 1971; Nordstoga, 1972), in dogs (Plowright, 1952; Basson, McCully, and Warnes, 1966), and in the cat and the ox (Schuster, 1925), although in the last cases the organism was not definitely identified. Only two acceptable cases of systemic infection in man have been reported (Matsubayashi, Koike, Mikata, Takei, and Hagiwara, 1959; Margileth, Strano, Chandra, Neafie, Blum, and McCully, 1973).

In 1964 it was believed that Encephalitozoon belonged to the family Nosematidae and it was proposed that the organism affecting mammals be re-named *Nosema cuniculi* (Wieser, 1964; Lainson, Garnham, Killick-Kendrick, and Bird, 1964). Recent studies, however, by Cali (1971), Shadduck and Pakes (1971), and Sprague and Vernick (1971), comparing the microsporidium with the type species for the genus Nosema (that is, *Nosema bombycis*—the cause of silkworm disease) have revealed differences in the developmental cycle. A return to the original name *Encephalitozoon cuniculi* was, therefore, proposed.

The only published case of infection of the animal eye is that of Perrin (1943) who found lymphocytic infiltration and a single accumulation of parasites in the retina of a spontaneously infected rat. A solitary case of such infection in the human eye was reported by Ashton and Wirasinha (1973) who found microsporidia in a corneal disc removed for a penetrating keratoplasty in an 11-year-old boy from Ceylon.

The purpose of the present communication is to report the first known example of cataract due to encephalitozoonosis, which occurred bilaterally in a spontaneously infected laboratory rabbit.

Material and findings

Bilateral cataract in a five-month-old rabbit (New Zealand white male; one of a litter of eight born 5 May 1975) was first noted by one of us (FGC, in connexion with an investigation not relevant here) and the animal was sent for further examination to the Department of Pathology at the Institute of Ophthalmology, London. No cataracts were observed ophthalmoscopically in the seven litter mates: the eyes of four of these submitted for histology showed no abnormality.

CLINICAL EXAMINATION

Right eye

The lens appeared clear apart from a triangular white opacity in the anterior cortex at 12 o'clock. No posterior synechiae or distortion of the pupil were seen and there was no other abnormality.

Left eye

Nodular fluffy white masses were seen within the anterior lens cortex at 4 and 8 o'clock, and posterior synechiae adjacent to these areas distorted the pupil. No other abnormality was seen.

HISTOLOGY

Macroscopical examination

The eyes were opened coronally and the anterior segments examined in normal saline at room temperature under the stereoscopic microscope. The findings confirmed the clinical examination (Figs 1 and 5). No other abnormalities were observed either in the anterior or posterior segments. The right anterior segment was sectioned in paraffin, while the left anterior segment and both posterior segments were sectioned in celloidin.

Microscopical examination

Right eye: anterior segment

The predominant pathological changes were to be seen in the lens which showed a focal cortical cataract on one

Address for reprints: Professor N. Ashton, FRS, Department of Pathology, Institute of Ophthalmology, Judd Street, London WC1H 9QS

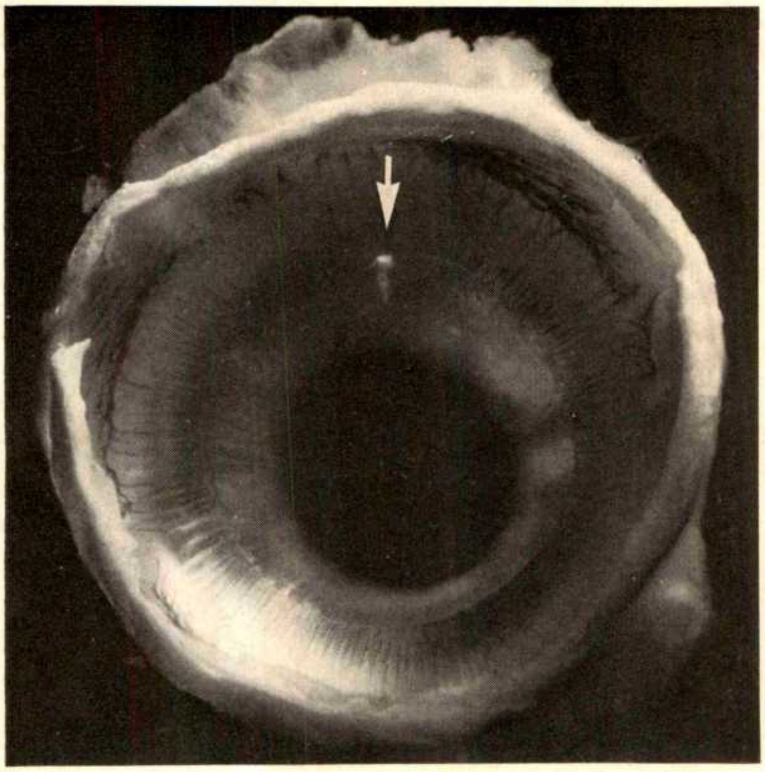

FIG. 1 *Right eye. Anterior segment, viewed postero-anteriorly. A triangular white opacity is seen at 12 o'clock (arrow) within anterior cortex of lens*

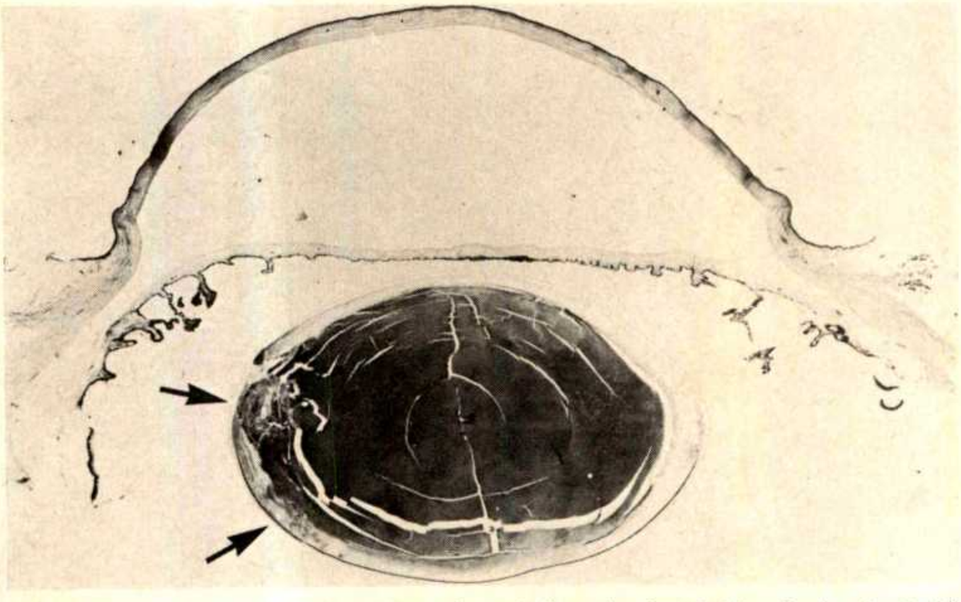

FIG. 2 *Right eye. Section of anterior segment. Arrows indicate site of cortical invasion by microsporidia. Note inflammatory infiltration of adjacent ciliary processes compared with unaffected processes on opposite side. Haematoxylin and eosin.* ×9

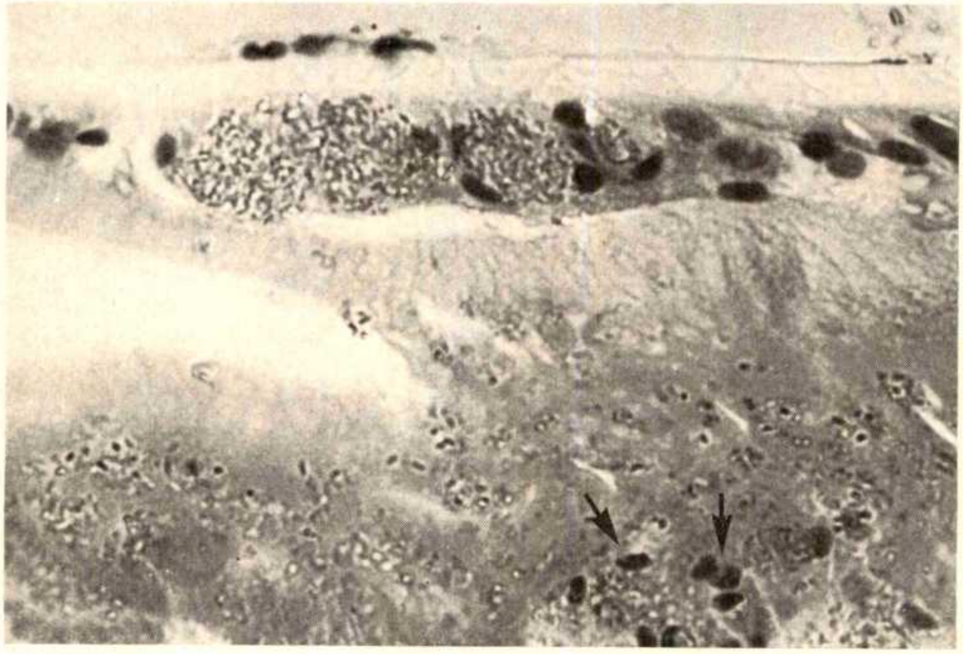

FIG. 3 *Right eye. Equatorial region of lens showing numerous refractile microsporidan spores within lens epithelium and lying free in adjacent cataractous cortical tissue together with degenerate epithelial nuclei (arrows). A few inflammatory cells are seen on surface of intact lens capsule. Haematoxylin and eosin.* ×780

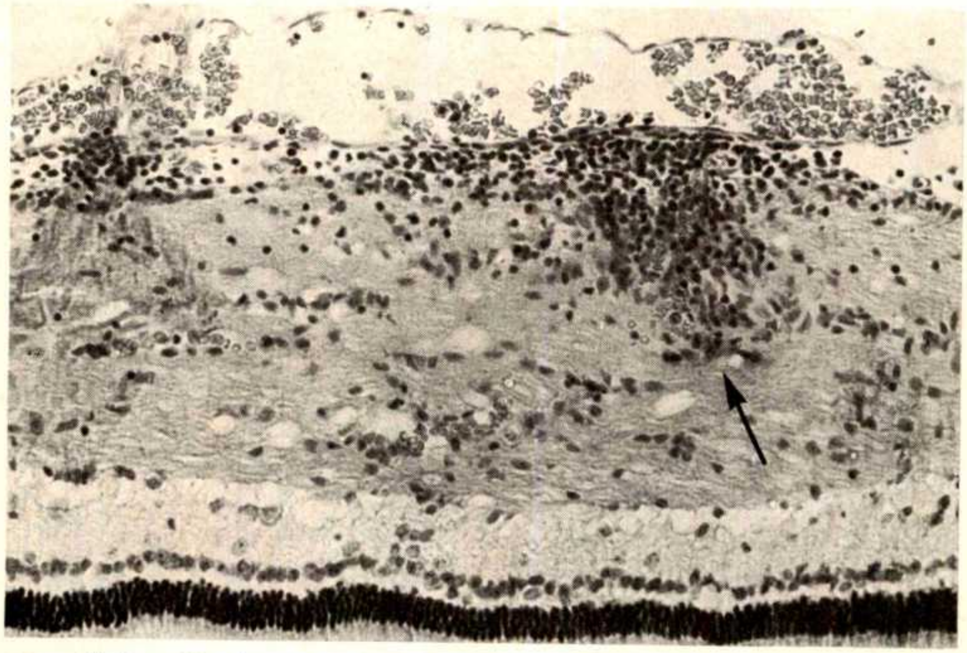

FIG. 4 *Right eye. Posterior segment showing a focal infiltration of monocytes in relation to a surface vessel and its intraretinal branch (arrow). No microsporidia were found outside lens. Haematoxylin and eosin.* ×260

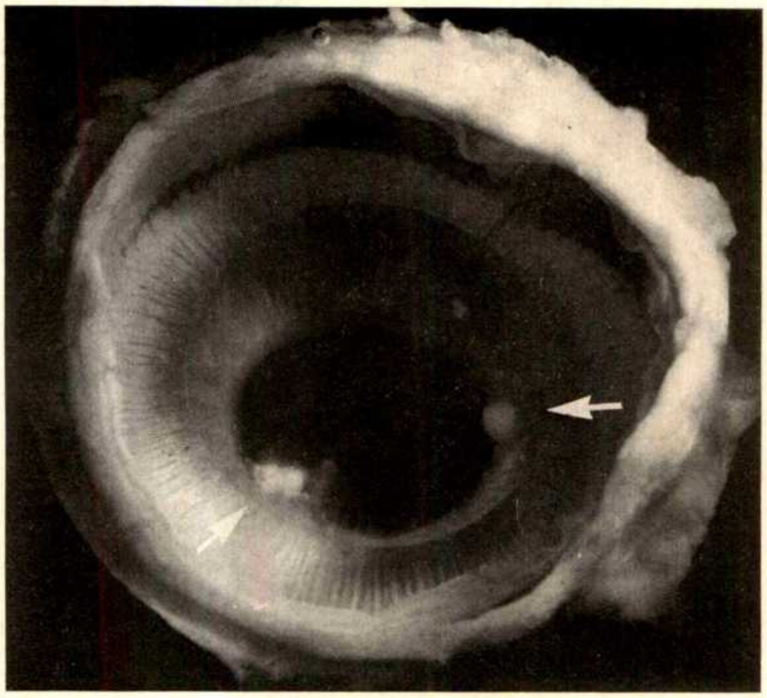

FIG. 5 *Left eye. Anterior segment, viewed postero-anteriorly. Nodular fluffy white masses are seen at 4 and 8 o'clock within anterior cortex of lens (arrows)*

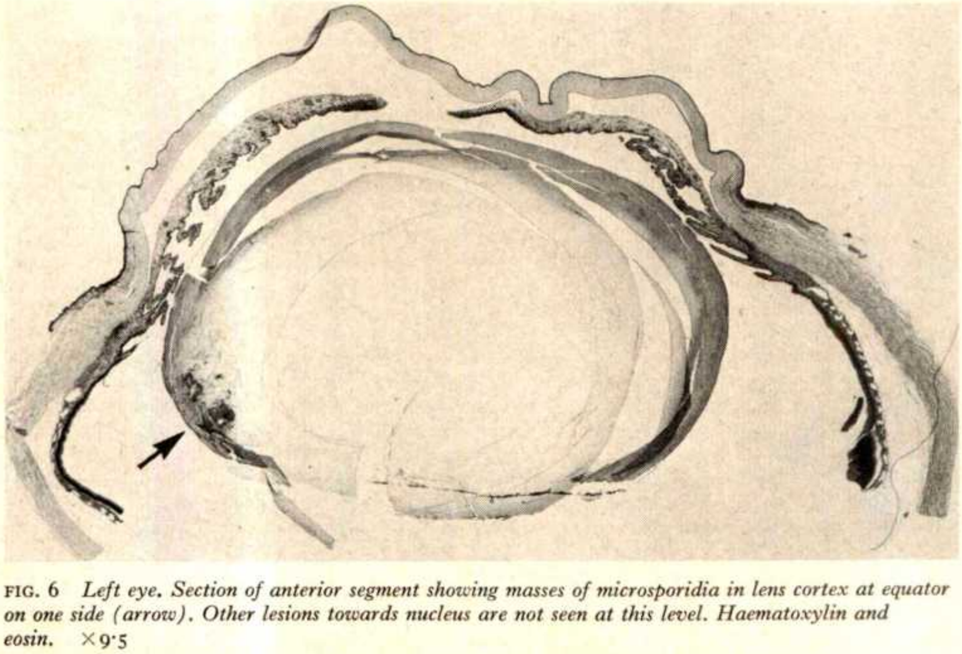

FIG. 6 *Left eye. Section of anterior segment showing masses of microsporidia in lens cortex at equator on one side (arrow). Other lesions towards nucleus are not seen at this level. Haematoxylin and eosin.* ×9·5

side of the section only and particularly at the equator, where several epithelial cells showed cytoplasmic aggregations of microsporidan parasites with highly refractile capsules and basophilic contents. These parasites were also seen within the cataractous equatorial tissue in irregular masses or lying free in eosinophilic fluid intermingled with degenerating epithelial nuclei. The adjacent ciliary body showed an intense inflammatory reaction extending into the posterior chamber. There was, however, only a mild inflammatory infiltration of the iris, and the ciliary body on the opposite side was almost normal. Only mononuclear cells were seen in the inflammatory reaction; there were no neutrophils or eosinophils and no parasites could be found outside the lens capsule (Figs 2 and 3).

Special stains

Periodic acid-Schiff and celestin blue failed to stain the organisms and no anterior polar cap could be identified. No breaks were found in the lens capsule in the region of the invaded epithelium. Giemsa and Gram stains gave variable results suggesting that some of the organisms were degenerate. Silver methenamine (Grocott-Gomori) stain showed masses of brownish-black microsporidia apparently empty.

Right eye: posterior segment

This showed a focal infiltration of monocytic cells on the surface of the disc and in the inner layers of the retina, especially around the surface vessels and intraretinal branches (Fig. 4). The choroid was normal except at the peripapillary margin where there was a mild inflammatory infiltration. In one minute focus in the retina posteriorly there was a sharply demarcated area of visual cell atrophy. No microsporidan parasites were found in any tissue in this segment.

Left eye: anterior segment

The lens showed focal cortical cataract particularly evident in the anterior and equatorial cortex on one side where masses of microsporidia could be seen within the liquefied lens material (Figs 6 and 7). In some sections they were associated with necrotic inflammatory cells, including a few polymorphonuclears, which had invaded the lens at two points where the capsule had ruptured (Fig. 8). Some sections showed parasites situated equatorially in relation to degenerate epithelial cell nuclei without inflammatory cells. Additionally, isolated granular aggregates resembling microsporidia were seen throughout the anterior cortex and near and within the lens nucleus (Fig. 9); occasionally these masses were calcified. The posterior pole of the lens was not invaded by cells or parasites. There was an inflammatory reaction in the anterior uvea, particularly intense at the pupillary margin and at the ora serrata. As in the case of the right eye, no parasites were found outside the lens.

Special stains

Periodic acid-Schiff and haematoxylin (PASH) stain showed basophilic nucleoplasm but no periodic acid-Schiff-positive reaction; periodic acid-Schiff and celestin blue and toluidine blue showed no specific staining of the microsporidia. Giemsa and Gram stains showed refractile capsules with blue contents, but the staining was variable. Silver methenamine (Grocott-Gomori) stain provided the best method for demonstrating the parasites; they stained black and were associated with crystalline debris (Fig. 10).

Left eye: posterior segment

This showed essentially similar changes to those of the right eye.

ELECTRON MICROSCOPY

A 10 μm celloidin section from the left lens was lightly stained with haematoxylin and examined in water under a dissecting microscope. The affected area containing the parasites was dissected out with micro-instruments and the celloidin was removed, the specimen rehydrated, postfixed in 1 per cent buffered osmium tetroxide, processed, and embedded in epoxy-resin. Thick flat sections were cut, using an LKB ultrotome 3, stained with toluidine blue and areas were selected for thin sectioning. These sections were examined with a Joel JEM 100 C electron microscope. A diagram illustrating the known ultrastructure of a microsporidan spore is shown in Fig. 11.

Electron micrographs showed large numbers of thickly encapsulated structures containing degenerate electron-dense material and an even larger number of thinly encapsulated cells resembling respectively mature and immature microsporidan spores lying in a coarsely granular matrix containing irregular homogeneous masses (Fig. 12). The mature spores ranged between 2·8 × 1·1 μm and 1·6 × 0·8 μm, this variability probably being due to the level and angle at which the individual spores were cut. The mature spores were oval, comma-shaped or round in cross-section and showed a thick electron-lucid wall with an outer and inner electron-dense membrane. Because of the formalin fixation little could be definitely identified in the internal structure, but the shrunken contents occasionally showed an irregular hole which might represent the posterior vacuole. A structure resembling a polaroplast could sometimes be identified lying anteriorly either as a dense or laminated area. An anterior vacuole in place of the supposed polaroplast was occasionally seen and a dense area, possibly the nucleus (sporoplasm, germ, or plamont), lay centrally. In some parasites profiles resembling a coiled filament or tubule with an electron-dense core could be seen. The sporonts appeared as simple oval, round or comma-shaped structures with thick membrane-bound homogeneous moderately electron-dense contents and occasionally with coarsely granular material, which sometimes extruded into the surrounding matrix and might have been the source of the granular material previously noted (Figs 13, 14, and 15).

It must be emphasized that the poor fixation and degenerative nature of this tissue makes a certain diagnosis impossible. Moreover, vacuoles of the order

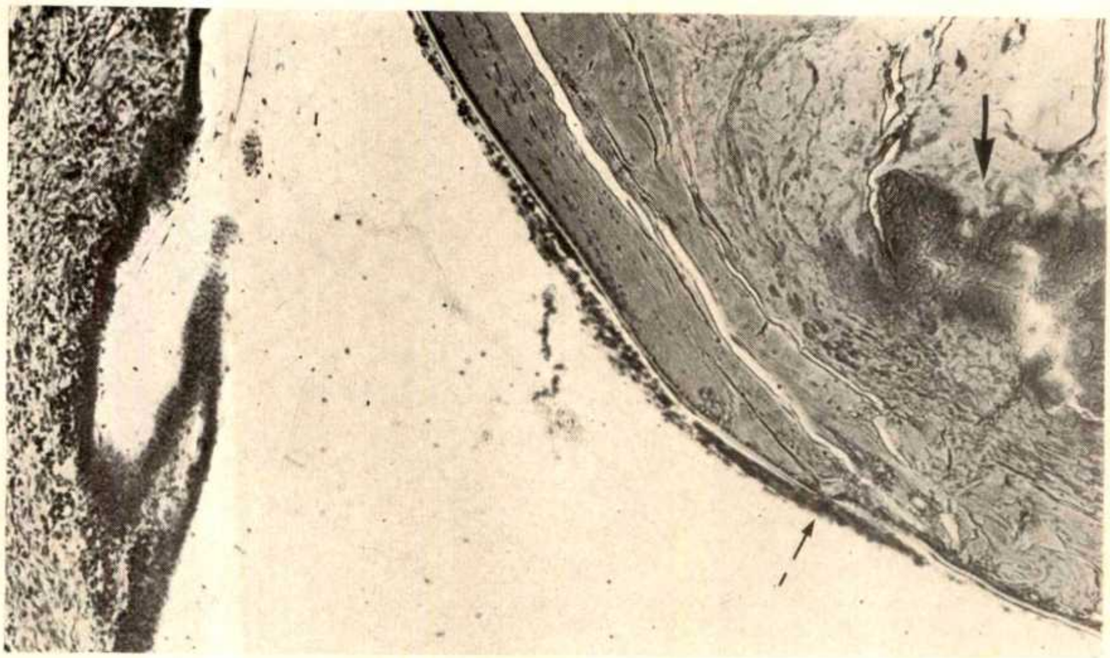

FIG. 7 *Left eye. Anterior segment. A mass of microsporidia lies within cataractous cortex of equatorial lens (thicker arrow) and inflammatory cells cover lens capsule which shows a small rupture (thinner arrow). A monocytic inflammatory reaction is present in ciliary body and inflammatory cells are scattered throughout posterior chamber. Haematoxylin and eosin.* ×72

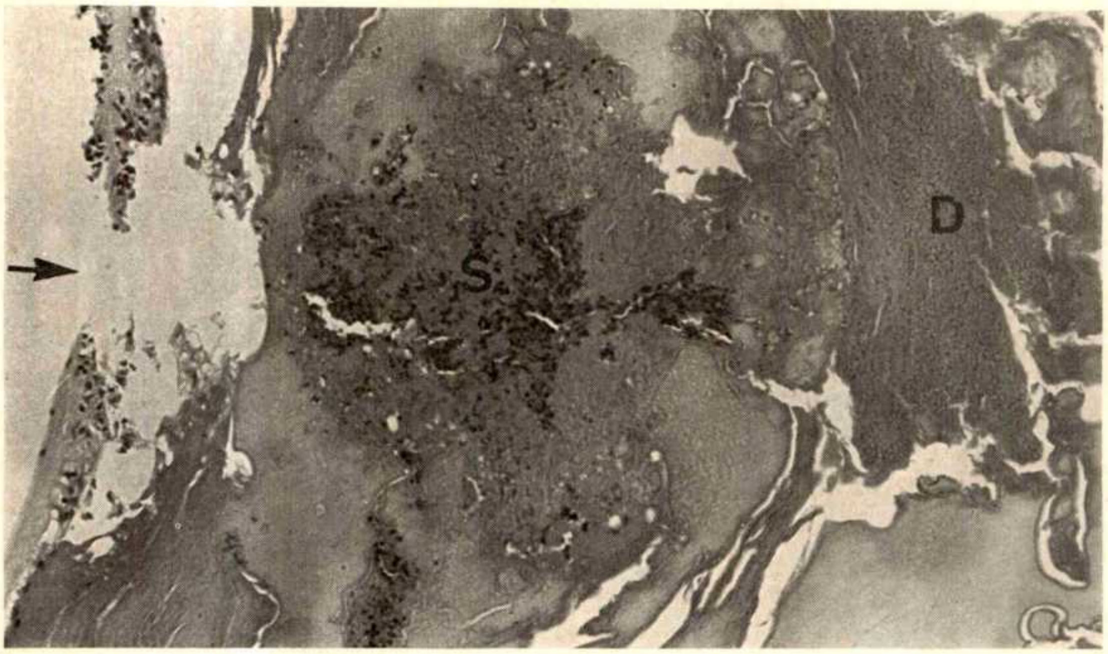

FIG. 8 *Left eye. Equatorial region of lens. Two masses of microsporidia lie within cortical cataract. Inflammatory cells have invaded the more superficial mass (S), entering through a rupture in capsule (arrow). The deeper mass (D) is free from inflammatory cells suggesting that capsule rupture was due to a secondary inflammatory invasion rather than a portal of entry for parasities. Haematoxylin and eosin.* ×180

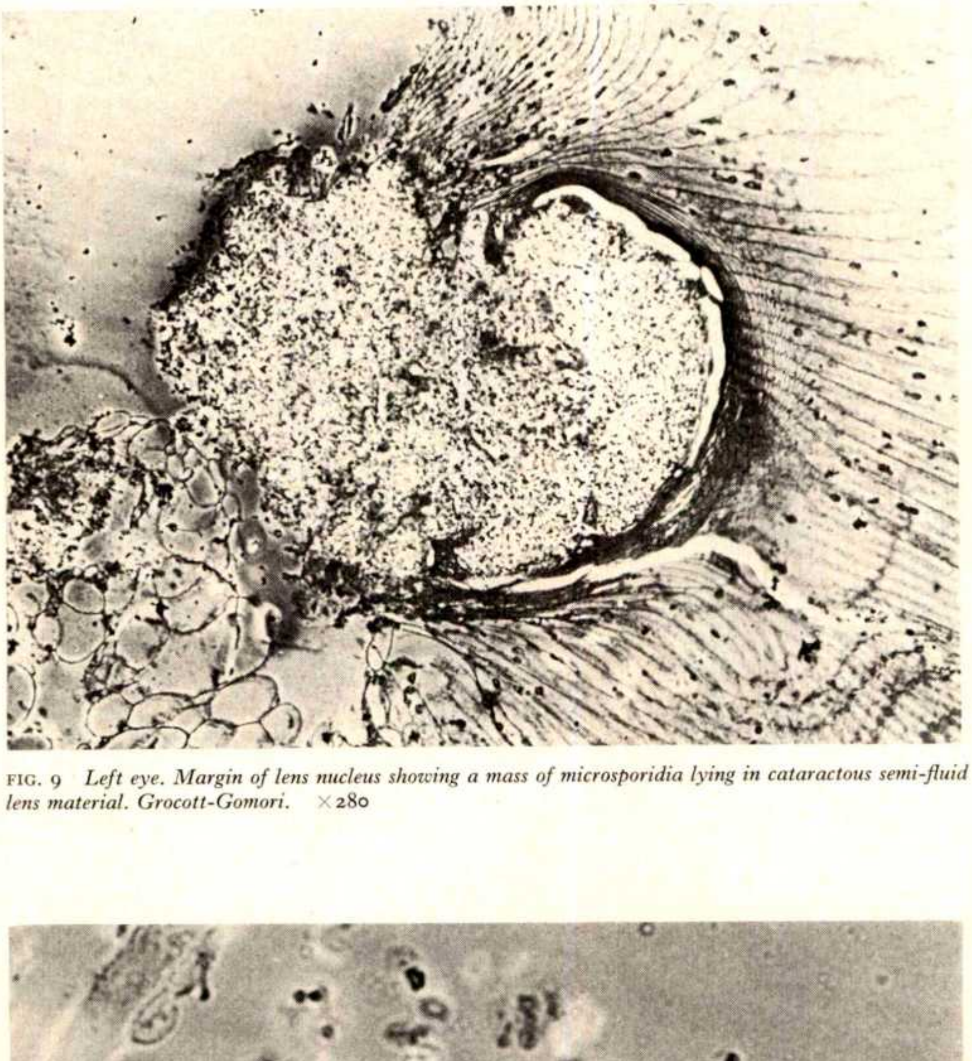

FIG. 9 *Left eye. Margin of lens nucleus showing a mass of microsporidia lying in cataractous semi-fluid lens material. Grocott-Gomori.* ×280

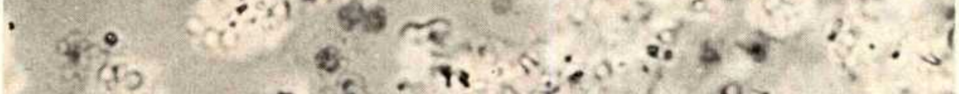

FIG. 10 *Left eye. Numerous microsporidan spores seen within the lens. The characteristic oval, round and comma shapes of the argyrophilic and refractile spore capsules can be seen. Grocott-Gomori.* ×1800

and size of microsporidia and argyrophilic granules are often seen in normal and cataractous lenses as fixation artefacts or pathological break-down products. Great care is needed in differentiating them from degenerate microsporidia especially as the two were seen to occur together in this rabbit's lenses. The vacuoles, some of which are due to shrinkage of lens interlocking processes and especially resemble microsporidia (Fig. 16), may be differentiated by their variability in size and their failure to take up silver stains. The ultrastructural appearances are the final arbiter and in the case here reported are strongly suggestive of microsporidia as illustrated by Lom and Vavra (1963a, b) and Sprague and Vernick (1968) and closely resemble those described for *Encephalitozoon cuniculi* (Petri and Schiødt, 1966; Margileth and others, 1973). Complete proof would have been the unequivocal demonstration of the polar filaments, whereas in our electron micrographs these could be only vaguely discerned. Nevertheless, we believe the correct diagnosis to be bilateral cataract due to *Encephalitozoon cuniculi* with reactive anterior uveitis and retinal perivasculitis and will proceed to the discussion on the basis of this conclusion.

Discussion

This example of bilateral cataract due to encephalitozoonosis in a spontaneously infected laboratory rabbit raises a number of interesting points. The fact that it has only now been recognized suggests that it is probably a rarity, and the bilateral involvement without injury to the ocular envelope indicates an origin from systemic infection, but as this diagnosis was not suspected clinically other organs were not examined. Since it has been reported that microsporidia are apparently unable to penetrate Descemet's membrane (Ashton and Wirasinha, 1973) it might be inferred that a mature lens capsule would also form a barrier, suggesting that the microsporidia gained entry to the lens at an early stage of intrauterine development before the capsule was fully formed (the two small ruptures seen only in the lens capsule of the left lens were likely to be due to a secondary inflammatory invasion). Vertical transmission of encephalitozoon is thought to occur (Levaditi, Nicolau, and Schoen, 1924; Perrin, 1943; Nelson, 1967) and has been strongly supported experimentally (Hunt, King, and Foster, 1972).

The equatorial preponderance of the infection and the associated degenerate epithelial cells suggest that the parasites probably invaded the lens epithelium in this region, as actually observed in some sections, and were carried into the lens as the fibres developed. Here it is improbable that the microsporidia would long survive since they are very simple organisms devoid of organelles and containing little besides the genome, which is injected via the filament into the host cell, so resembling viruses (phages) in this respect rather than protozoa (Sprague and Vernick, 1968). Unless the enzymes of biological oxidation are located in the spore membranes (Liu, 1973, 1975) microsporidia would seem to be entirely dependent upon the metabolism of fully functional cells, which the epithelial cells of the lens cease to be as they transform into fibres with loss of nuclei and organelles.

An intriguing question is why the parasites were found only within the lens; the inflammatory reaction outside the capsule in the anterior and posterior segments probably resulted from diffusion of a toxin from the intralenticular colonies. Such a selective affinity for lens epithelium, however, is not unique as it is seen also in many cases of the rubella syndrome where cataract may similarly be the predominant or only ocular abnormality. Another explanation could be that the microsporidia within the lens as opposed to those without, are protected from immune reactions.

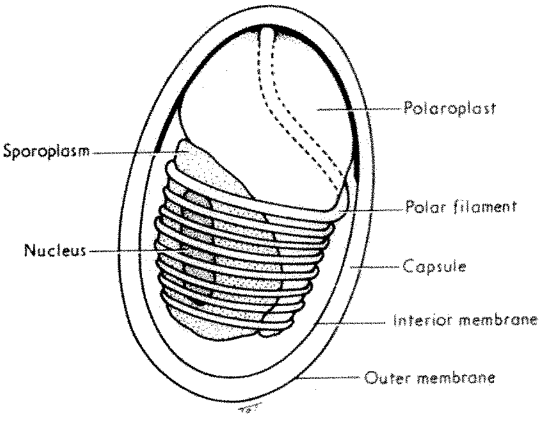

FIG. 11 *Diagram of the fine structure of a microsporidan spore (after Kudo and Daniels, 1963) showing thick capsule and characteristic tubular coiled polar filament passing through polaroplast, which may appear laminated, granular, or vacuolar and which is responsible for ejecting the filament. A nucleus lies within the sporoplasm*

Encephalitozoon cuniculi bear a close resemblance to *Toxoplasma gondii* and, although taxonomically not closely related, they can readily be mistaken for each other, a point of great importance in microscopical differential diagnosis (Margileth and others, 1973). Since both these parasites may be transmitted transplacentally the question arises whether *Toxoplasma* could similarly be directly responsible for cataract. The lens is usually undamaged in ocular toxoplasmosis and in cases where cataract occurred it was regarded as secondary to the inflammatory reaction (Dekking, 1949; Glees,

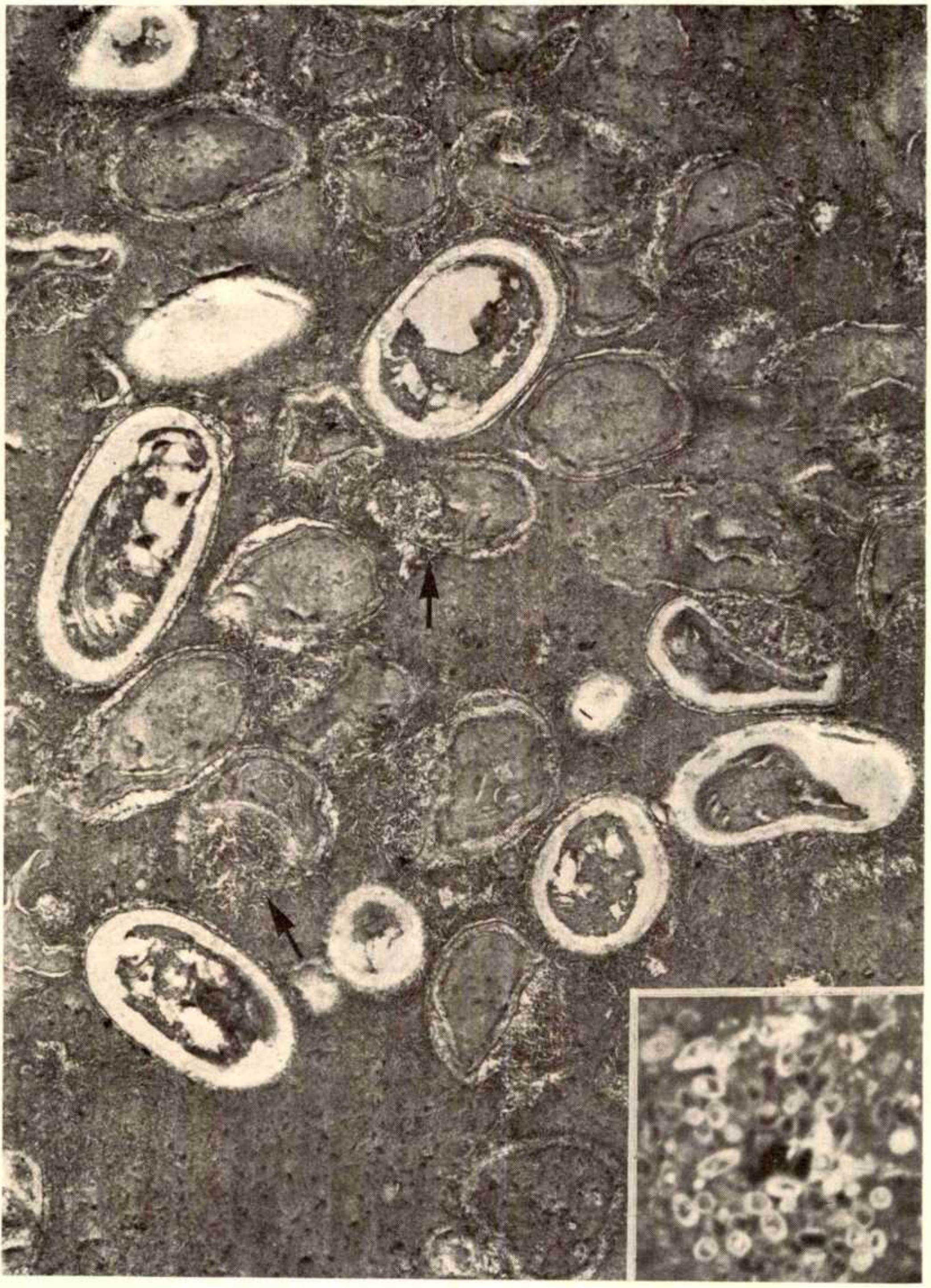

FIG. 12 *General view of microsporidia in left lens showing a few vacuolated and thickly encapsulated mature spores and numerous sporonts lying in homogeneous matrix containing coarsely granular material which is also seen within the sporonts (arrows). Electron micrograph.* ×15 000. *Insert shows light microscopy of epon section of this area.* ×2880

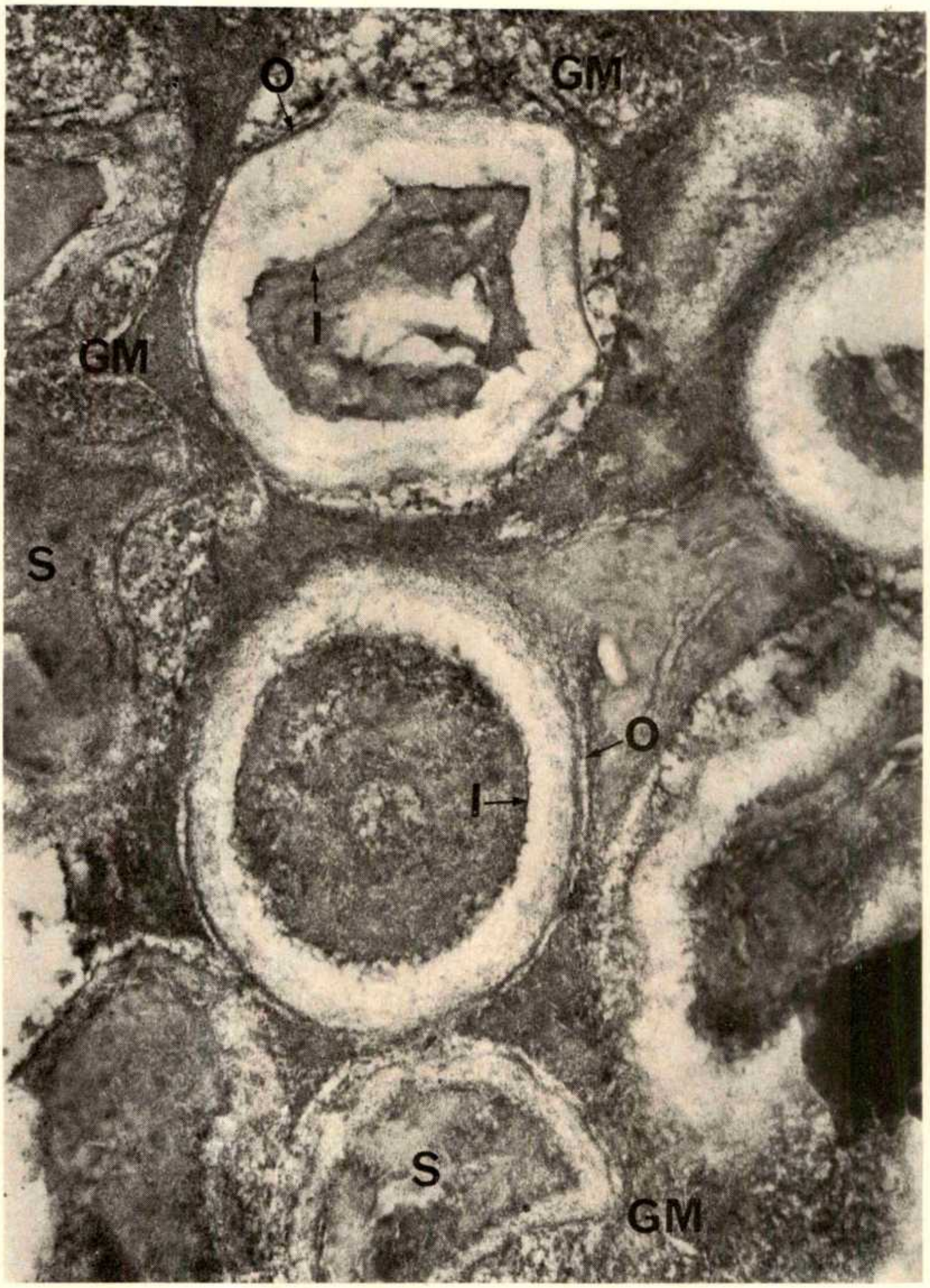

FIG. 13 *High power view of microsporidia. Fully mature spores show thick electron lucid capsule with its inner (I) and outer (O) membranes. Coarse granular material (GM) is present within and around sporonts (S) which show earlier stage of encapsulation. Electron micrograph.* ×48 000

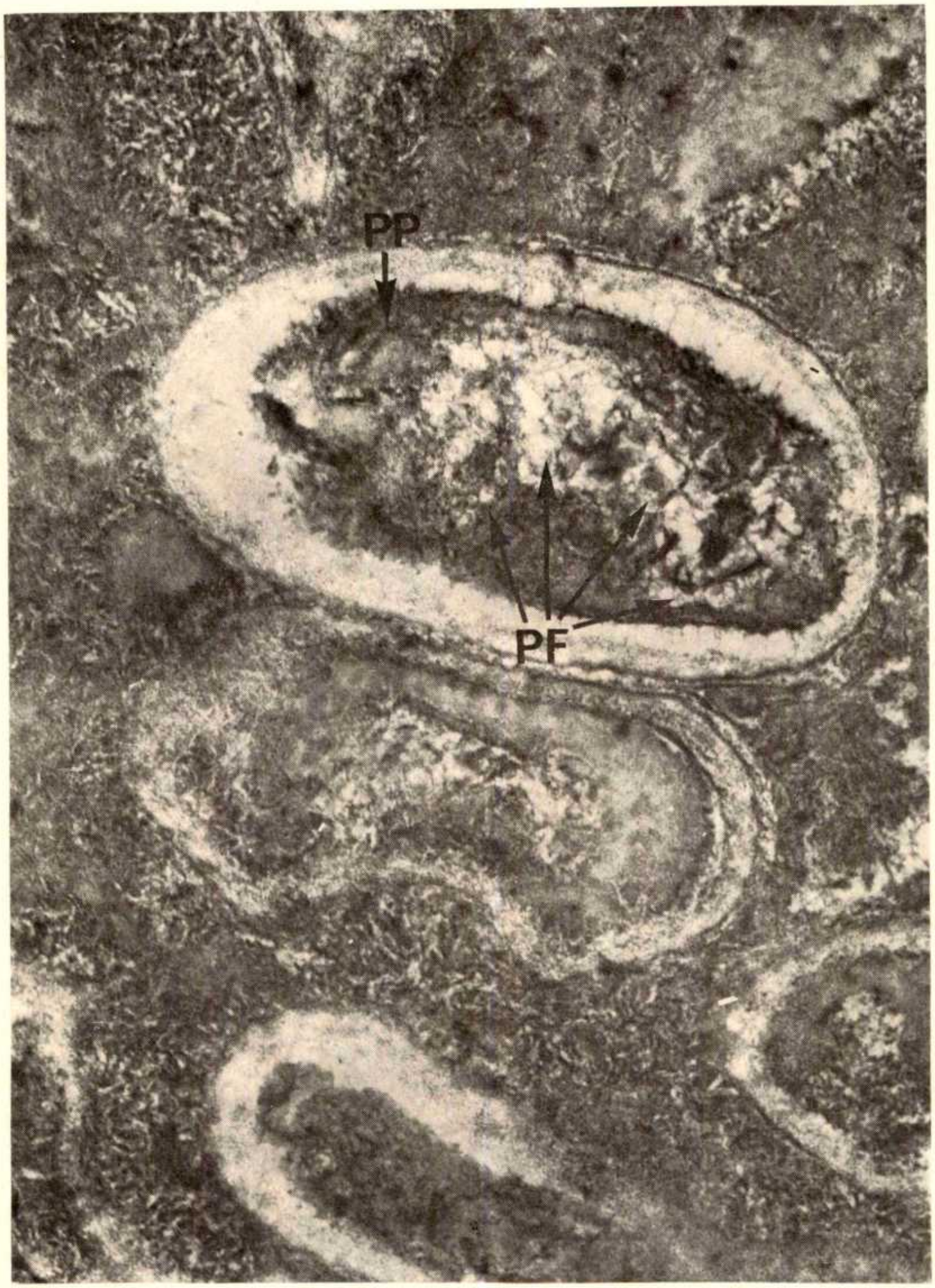

FIG. 14 *Another area showing a spore in which laminated polaroplast (PP) might possibly be discerned anteriorly and indistinct circular and convoluted profiles (PF) may represent coiled polar filament. Electron micrograph.* ×48 000

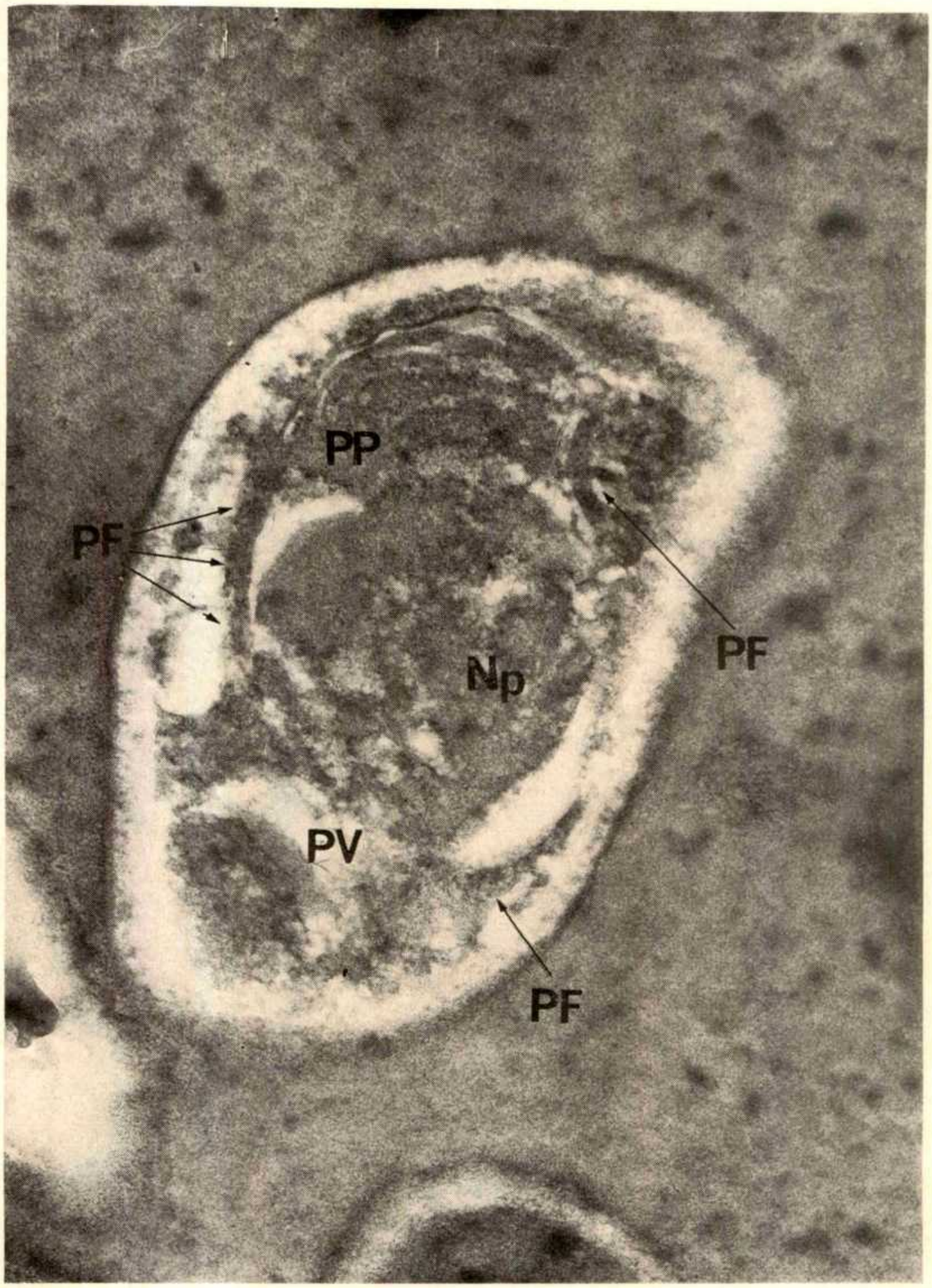

FIG. 15 *Higher power view of a microsporidan spore. Laminated polaroplast (PP), fragments of polar filament (PF), nucleoplasm (Np) and posterior vacuole may possibly be discerned (PV). Electron micrograph.* ×70 000

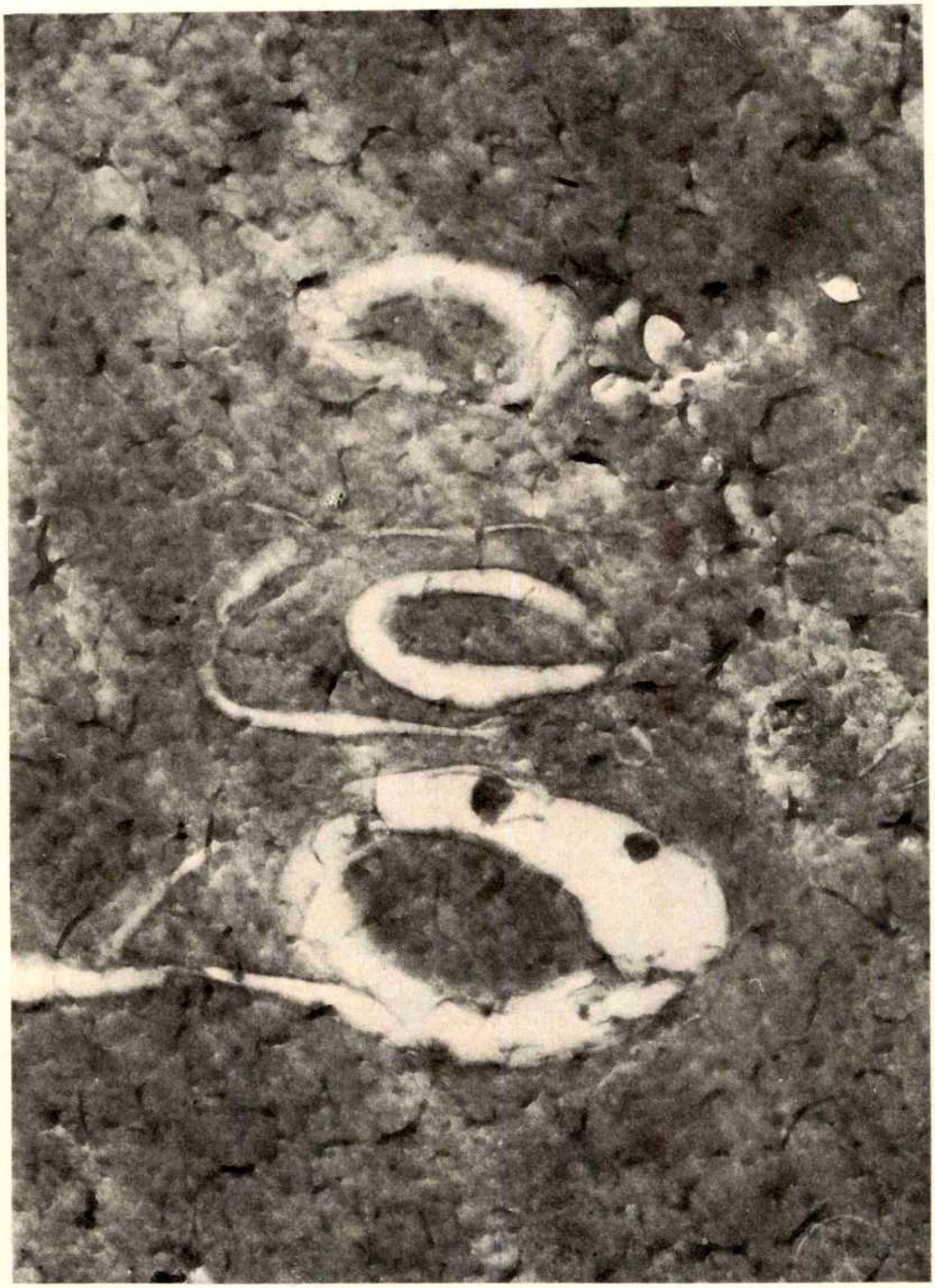

FIG. 16 *Cataractous lens showing profiles superficially resembling microsporidia, but which are of variable size. The pseudocapsules are due to gross widening of intercellular space between a lens cell and interlocking processes of adjacent cell. Electron micrograph.* × 33 000

1953; Lavat, 1953): in rats where congenital cataract was the only manifestation of toxoplasmosis it was attributed to toxins produced by the parasites (Giroud, Giroud, and Martinet, 1954). There is only one report in the literature suggesting direct invasion of the lens: Ourth (1971) claimed to have demonstrated *Toxoplasma gondii* in 30 per cent of a series of cataractous human lenses using the direct fluorescent antibody technique. This question was carefully re-examined by Davies, Fleck, and Rahi (1973) who could not agree with Ourth's interpretation, believing that the particles he described were fragments of lens epithelium disrupted during homogenization. These investigations, however, were mainly concerned with senile cataract, so that whether or not protozoa play any direct role in the aetiology of congenital cataract in man, although extremely unlikely, still remains unknown.

Summary

Bilateral cataract due to a microsporidan believed to be *Encephalitozoon cuniculi* (also called *Nosema cuniculi*) is described as an incidental finding in a laboratory rabbit. The route of infection and the significance of the findings are discussed. This is apparently the first report of cataract due to this cause.

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Cataract after exposure to non-ionizing radiant energy

MILTON M. ZARET, WENDY Z. SNYDER, AND LEO BIRENBAUM
From New York University Medical Center, Departments of Ophthalmology and Physiology, and Polytechnic Institute of New York, Department of Electrical Engineering and Electrophysics

The case reports that follow suggest that infrared radiation emitted from an electric oven and stove could be a contributory or aetiological factor in the differential diagnosis of cataracts.

During the past 30 years, there has been a constant increase in the number of devices such as diathermy machines, microwave ovens, and electric stoves which emit radiant energy. While industrial heat (infrared) cataract in glassblowers and furnace workers was first recognized nearly 200 years ago (Wenzel, 1786), lens damage caused by microwave irradiation is a disease related to modern technology (Daily, Wakim, Herrick, Parkhill, and Benedict, 1952; Richardson, Lomax, Nichols, and Green, 1952; Shimkovich and Shilyaev, 1959; Zaret, 1964; Bouchat and Marsol, 1967; Kurz and Einaugler, 1968; Zaret, 1974a, b). In both types of cataract the aetiology of the lesion has usually been explained in terms of thermal damage from absorbed radiation. In view of the long latent period often observed between exposure to repeated, subliminal doses of infrared or microwave radiation and the appearance of clinical cataracts, it has been suggested (Duke-Elder, 1972a) that single exposures to such radiations, which are not of themselves harmful, may become hazardous if repeated sufficiently often. Furthermore, the shorter the interval between subthreshold irradiations, the more likely it becomes that such lens changes ultimately will develop.

In this paper we present two case reports, that of a wife and husband, with different histories of exposure to non-ionizing radiant energy. Each individual developed a specific type of ocular lesion relatable to exposure. The woman, who received medical diathermy treatment for a back injury and, in later years, cooked on an electric oven and range, developed capsular cataracts in both eyes; the delayed type of cataractogenesis after diathermy therapy, instead of remaining latent, appeared to be exacerbated and hastened by additional exposure to infrared emission from the cooking device. Her husband, who had a longer history of exposure to the electric range only, developed first a retinopathy and later a lens capsule opacity both resembling injury from non-ionizing radiation. Clinical and histological evaluation of the cataractogenesis and capsulopathy will be discussed.

Case reports

CASE 1

This 46-year-old White woman was first examined on 4 January 1975, having been referred because of unusual cataracts. During the previous two years, her eyeglasses had been changed at approximately three-monthly intervals because of changes in refractive error and an intermittent esotropia. Visual acuity was correctable to 20/20 minus for the right eye and 20/30 minus for the left eye; her only complaint regarding clarity of vision was that it appeared as if she were looking through a transparent curtain with her left eye.

Slit-lamp examination revealed a large, irregularly outlined, honeycombed capsulopathy involving more than half of the posterior surface of the lens. A few regions of vesiculation and opacification were present in the lens substance at its interface with the capsule. Thus, all of the disease was limited to the posterior lens capsule and adjacent, contiguous surfaces of the lens substance. This form of capsular cataract was present bilaterally, being slightly more extensive in the left than the right lens. Fig. 1 is a photograph of the left eye taken at the time of this examination.

There was nothing in the patient's history to suggest an aetiology except exposure to a course of medical diathermy as therapy for back pain approximately 15 years earlier.

The diagnosis was incipient, delayed radiant energy cataract. The patient was advised that this type of cataract ordinarily would lie dormant or progress very slowly over a time period measured in years, that no treatment other than surgery was available, that surgery was not indicated at this time, and that she should avoid any additional exposure to radiant energy, especially non-ionizing radiation such as from medical diathermy or microwave ovens. She was instructed to return for a follow-up examination after an interval of three to six months because no significant changes were expected to occur sooner.

However, within two months the patient had observed both a further decrease in vision which now made driving at night hazardous and increased difficulty in reading because the esotropia recurred more frequently. Therefore, she returned for re-examination on 15 March. At this time the best correctable visual acuity of the left eye was reduced to 20/40 minus due to progression of the cataractous changes. It was also noted that after

Address for reprints: Milton M. Zaret, MD, 1230 Post Road, Scarsdale, New York 10583, USA

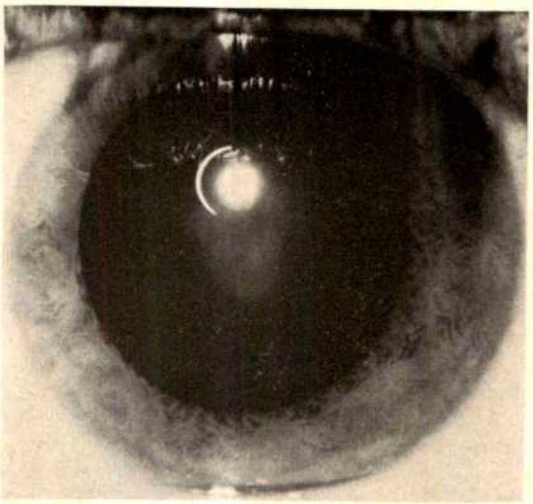

FIG. 1 *Lens photograph, Case 1, left eye. Note cataract formation limited to posterior surface of lens*

instillation of mydriatics the pupils did not dilate well; this is not an uncommon, late finding in non-ionizing radiation cataracts, occasionally indicating the formation of posterior synechiae located peripherally, at the point where the iris first lies in apposition with the anterior bulge of the lens. This suspicion of synechiae was confirmed at cataract surgery performed on 15 April, when it was necessary to perform posterior synechiotomies to free the lens from iridial adhesions in order to extract the cataract without rupturing the lens capsule.

By 9 August 1975, the cataractous process in the right eye had also become more extensive, the lesion now involved most of the posterior surface of the lens and, in addition, a marked capsulopathy had become evident at its anterior surface. The patient's complaints were hazy vision and intermittent diplopia. Visual acuity was reduced to 20/50 plus or minus.

Cataract extraction was performed on the right eye on 20 August. At surgery, the anterior capsule was found to be adherent to the iris and the posterior capsule was adherent to the face of the vitreous. The adhesions were lysed and the lens was then delivered from the eye intracapsularly. After surgery, visual acuity was correctable to 20/20 plus in each eye separately and the resultant restoration of the ability for fusion corrected the intermittent esotropia.

In view of the unusually rapid development of this patient's cataracts, which took place over a period of months rather than years, an investigation was undertaken to determine whether some additional radiant energy source in the patient's environment could have been providing repeated, covert exposures, thus being a contributory factor. The only suspicious element was that, since her marriage on 8 December 1973, she had used an electric range and oven. Both she and her husband worked and, as he returned home earlier than she, frequently he would cook the dinner. For this reason, it was decided to examine his eyes for signs of radiant energy effects.

CASE 2

This asymptomatic 55-year-old man was first examined on 3 May 1975. His medical and occupational histories were negative regarding serious illness or significant exposure to non-ionizing radiation.

The examination findings were physiological except for ophthalmoscopy. In the left eye, the macula exhibited pigmentary changes, generalized hyperpigmentation with a few scattered minute areas of depigmentation, a finding seen rarely in general population groups but not infrequently in workers where the occupational environment has an increased ambiance of photic energy (infrared and high intensity light environments) (Duke-Elder, 1972b; Zaret, 1972). Also in the left eye, a small area of pigmentary, degenerative change was present superiorly between the macula and optic disc. These changes are shown in Fig. 2, a retinal photograph of the left eye. In the right eye, two minute areas of depigmentation, each about 0·1 mm in diameter, were found in the inferior region of the macula. By slit-lamp examination, both lenses were entirely physiological.

After an interval of six months, the patient was re-examined on 22 November 1975. His visual acuity had remained correctable to 20/20 in each eye. However, the maculopathy had become more marked in both eyes. More importantly, by slit-lamp biomicroscopy a small area of capsular opacification measuring about 1·0 mm in largest diameter had now become apparent at the posterior surface of the left lens. These retinal and lens findings are compatible with frequently repeated exposure to non-ionizing radiation.

In view of the implication that the electric oven and range could have served as a harmful, covert source of radiant energy exposure for both patients, being contributory to Case 1 and causal for Case 2, measurements were made of its emissions.

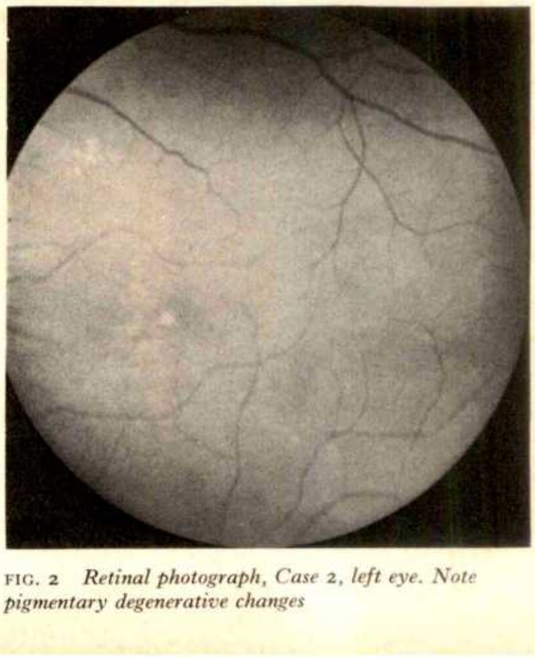

FIG. 2 *Retinal photograph, Case 2, left eye. Note pigmentary degenerative changes*

MEASUREMENTS OF ELECTRIC OVEN AND RANGE EMISSION

Measurement of the radiant energy emission was accomplished by using a calibrated Eppley thermopile and a Keithley model 150B microvolt ammeter.

Irradiation measurements of the electric oven with the controls set at the 'broil' position were taken at a distance of 30·4 cm in front of the door. The values were 24 mW/cm² with the door closed and 97 mW/cm² with the door open.

The electric range had four burners, two in front and two at the back. Measurements were taken at a distance of 45·7 cm in front of the range. With one front burner on 'high', the irradiation flux was 57 mW/cm². With one front and the ipsilateral rear burner on 'high', the measured emission was 97 mW/cm². No measurements were made with all of the stove sources emitting, as such a flux of radiant energy would have exceeded by far the solar constant, an obviously hazardous condition for direct exposure of the eyes.

Results

HISTOLOGICAL FINDINGS

After cataract extraction the right lens was immediately placed in 4 per cent glutaraldehyde buffered with 0·1 mol/l sodium cacocdylate for 120 hours at room temperature (approximately 24°C). The tissue was rinsed in buffer with 4 per cent sucrose, sliced into anterior and posterior segments and postfixed for four hours in 1 per cent osmium tetroxide buffered with the cacocdylate-sucrose medium. After further rinsing in buffer and dehydration in a graded series of alcohols, the tissue was trimmed and cut into small strips and embedded in epon. Thick (1 to 2 μm) sections were cut on a Porter-Blum (M-2) ultra-microtome, stained with 1 per cent methylene blue and photographed under oil (× 560) with a Zeiss photomicroscope.

Fig. 3 shows the anterior surface of the lens lying behind the iris. Note the posterior synechiae with pigmented precipitates deposited on the anterior lens capsule. The subcapsular epithelium appears vacuolated and several cell nuclei seem pyknotic. In Fig. 4 a more central area of the anterior surface of the lens is shown. Here, the non-uniform staining of the capsule is apparent and the subcapsular epithelium is vacuolated.

Figs 5 and 6 represent the posterior surface of the lens. In Fig. 5 note the irregular, outer surface of the posterior capsule and the vacuolization of the posterior cortex. The splitting of the capsule from the subcapsular cortex is an artefact. Fig. 6 shows the non-uniform staining of the posterior capsule. There appears to be a large area of subcapsular degeneration of the cortex as well as vacuolization of discrete areas. A close inspection of the inner surface of the capsule reveals that lens substance is adherent to it, thus obliterating the potential subcapsular space. Another feature of this apparent adhesion of the lens substance to capsule is that the lens substance at this site is more densely stained. Perhaps this may explain the earliest clinical appearance by slit-lamp biomicroscopy of capsulopathy in non-ionizing radiation cataract.

Discussion

The clinical findings and course for Case 1 suggest that the earlier exposure to medical diathermy radiation produced a covert, slowly progressing, pathological process which was later accelerated by repeated exposure to infrared radiation. Otherwise, there was an unusually short duration of time required for the full evolution of the non-ionizing radiation cataracts.

The histological appearance of the cataractous lens includes features previously described in experimental and clinical lesions produced after repeated, subliminal exposure to infrared or microwave irradiation. The pathological findings of the anterior surface of the lens—including pigment deposition on the anterior capsule, swelling and vacuolization of the subcapsular epithelium, and neighbouring lens fibres in association with posterior subcapsular vacuolization—are typical of of an infrared lesion (Vogt, 1930; Goldmann, 1932; Langley, Mortimer, and McCulloch, 1960). Vesiculation or honeycomb appearance at the posterior capsule and subcapsular cortex is more characteristic of medical diathermy or microwave-induced cataracts (Zaret, 1964; Bouchat and Marsol, 1967; Kurz and Einaugler, 1968; Zaret, 1974a and b). This patient exhibited both infrared and diathermy radiation findings. Thus it appears that the histological evaluation of the lens supports the clinical impression that the more recent infrared exposure was effective quickly because of earlier exposure from medical diathermy.

The pathogenic cause of non-ionizing radiant energy cataract is probably not as simple as some investigators have implied. For example, infrared rays are reported to be absorbed mainly by the pigment epithelium of the iris (Goldmann, 1932; Langley and others, 1960), and converted to heat which may damage the adjacent capsule and subcapsular epithelium of the lens. Local increase in temperature at the anterior surface of the lens, normally 1·5°C cooler than the posterior pole, can be produced experimentally with infrared radiation (Goldmann, 1932). However, the delayed-type of microwave cataract usually is observed at the posterior surface of the lens and can be produced experimentally more easily in albino than in pigmented rabbits (Daily and others, 1952). Here,

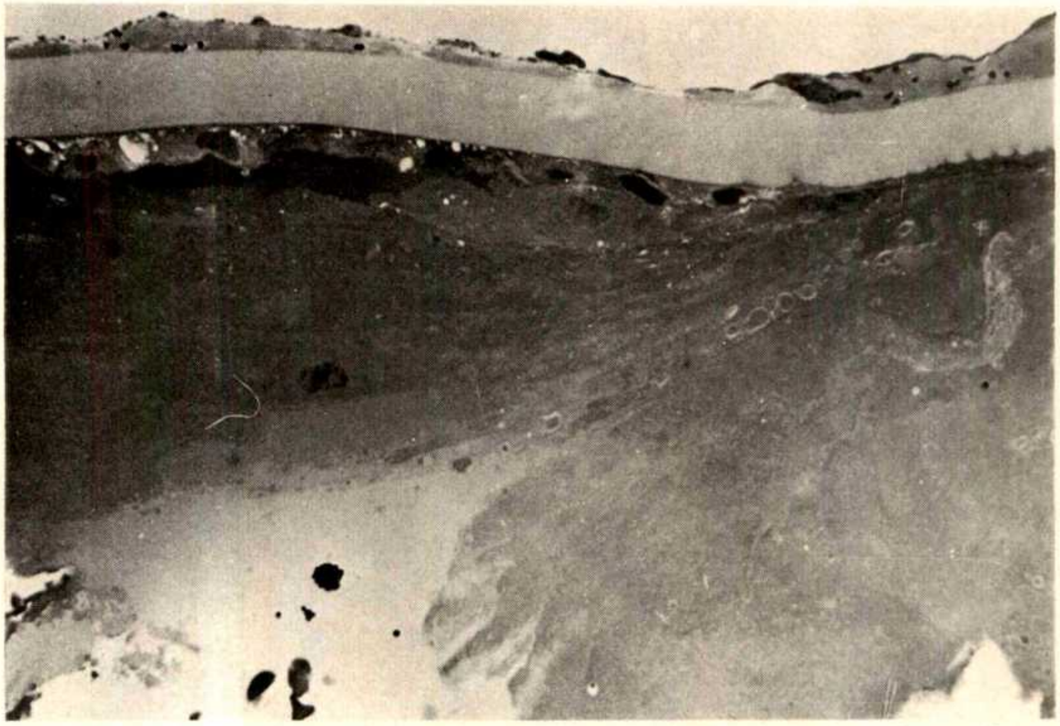

FIG. 3 *Anterior surface of lens, behind the iris (methylene blue, × 560). Note pigmented precipitates on lens capsule and vacuolization of subcapsular epithelium*

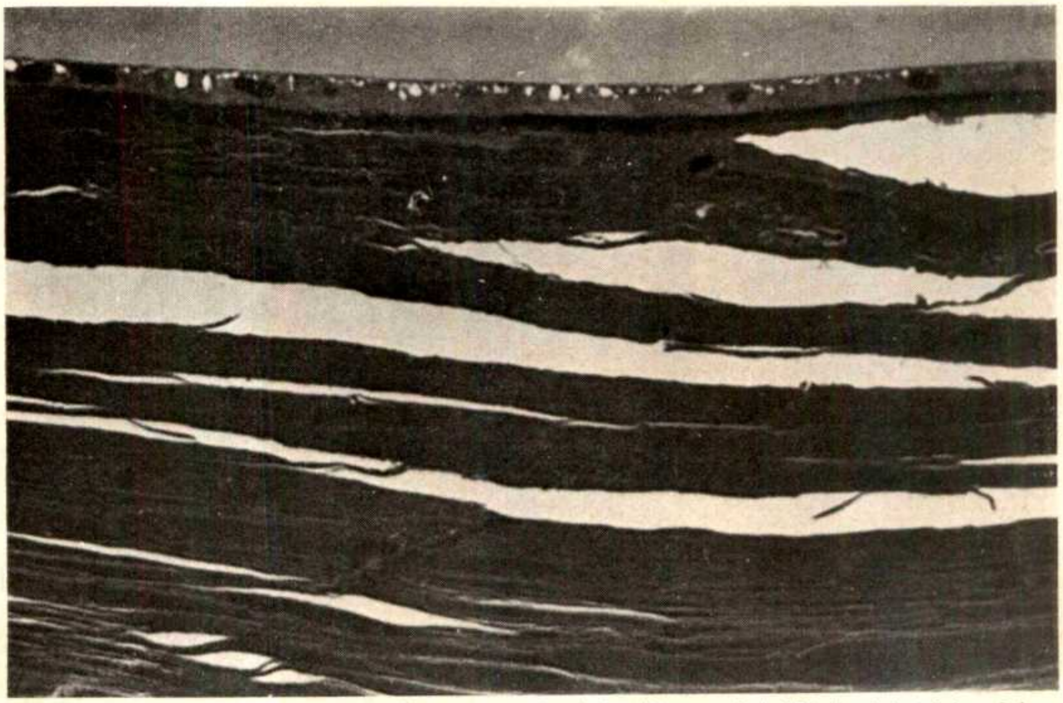

FIG. 4 *Anterior surface of lens, near pupillary aperture (methylene blue, × 560). Note banded staining of the capsule and vacuolization of subcapsular epithelium*

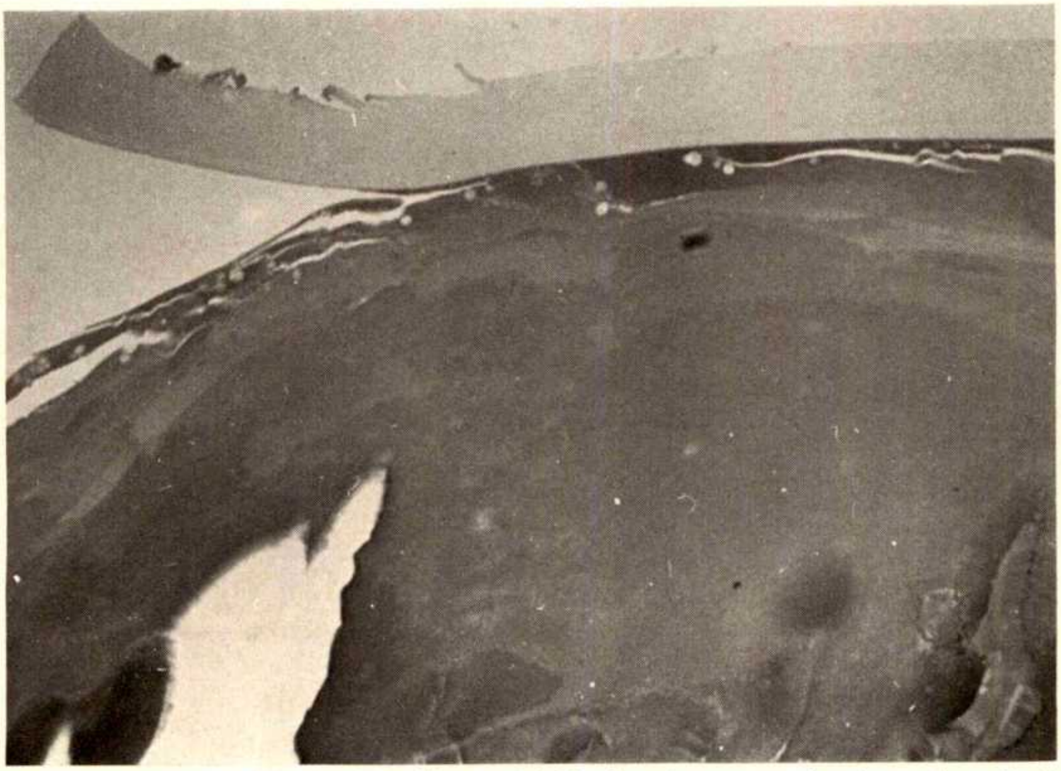

FIG. 5 *Posterior surface of lens (methylene blue, × 560). Note irregular, outer capsule surface, and vacuolization of subcapsular cortex*

a direct heat effect from absorption by the pigment of the iris seems unlikely.

There is a growing body of scientific data (Czerski, 1974) demonstrating that long-term, chronic, or frequently repeated exposure to low field intensities of non-ionizing radiation can produce non-thermal effects on man. These are not associated with recognizable signs or symptoms of whole or partial increases in body temperature. In the lens, the clinical observation of a long latent period measured in months or years between exposure and effect suggests that these lesions are not produced directly by a local increase in temperature during irradiation of the tissue. In addition, the adhesions between iris and lens capsule also develop later. These findings suggest that perhaps the radiant energy damages the lens capsule directly (Zaret, 1972), altering its permeability or elasticity, thereby disrupting normal protein metabolism in the adjacent lens fibres. The injured capsule and subsequent permeation of proteolytic products through it may result in a proteopexic adhesion to whatever adjacent tissues lie in contact with the lens. Such a process could explain the clinical findings of adhesions of the lens capsule not only to the iris but also to the face of the vitreous and thus provide a rationale for the delayed development of these adhesions.

In Case 2, the maculopathy is indistinguishable from that seen in radiational chorioretinitis after repeated exposure to infrared radiation over an extended period of time. However, it is more important to note that capsular opacification has just become evident in the left lens, indicating that cataractogenesis is at a very early stage. Although one would anticipate a slow progression of the radiational injuries should the exposures continue, as a preventive measure the patient was advised to discontinue unnecessary, further exposure to any intense source of radiant energy, including the electric oven and stove.

Summary

The case histories of two individuals exposed to thermal radiation emitted from an electric oven and range were presented. In one patient, earlier exposure to medical diathermy appears to have initiated delayed or late-appearing, capsular cataracts. Instead of the anticipated slow progression, the cataractogenesis was accelerated following recent, repeated exposure to the intense, infrared

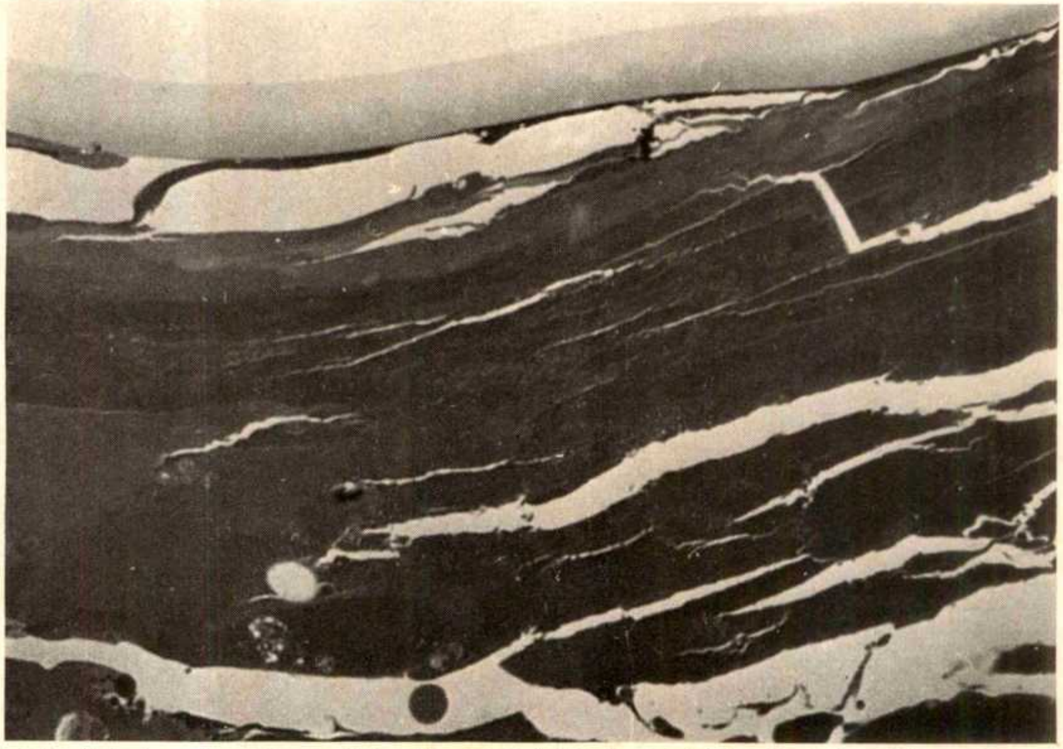

FIG. 6 *Posterior surface of lens (methylene blue,* × 560*). Note banded staining of capsule and degenerated areas of subcapsular cortex*

radiation. In the other patient, exposed solely to infrared radiation, a chorioretinal lesion indistinguishable from the type characteristically secondary to repeated, thermal radiation was observed. More recently, the earliest sign of thermal radiation cataractogenesis, capsular opacification, has become evident.

The widespread availability of radiant energy sources such as diathermy machines, microwave ovens, and electric ovens and ranges makes it imperative to examine carefully any possible hazards that may result from their use. With this in mind, radiant energy should be considered in the differential diagnosis of cataractogenesis.

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Keratometric changes after cataract extraction

DHANWANT SINGH* AND KIRANJIT KUMAR†
From the Rajindra Hospital, Patiala, India, and the Civil Hospital, Faridkot, India†*

Since Donders (1864) noticed that inverse astigmatism often occurred after superior section for an iridectomy or for cataract extraction, surgeons have differed about the type and number of sutures which produce least postoperative astigmatism. The present study, conducted in the Eye Department of the Rajindra Hospital, Patiala, was designed to try to resolve this question in relation to cataract wound closure.

Patients and methods

One hundred cases of cataract extraction were selected for study. In 50 cases (group A) the sutures were preplaced. Of these 50, 16 had one preplaced suture, 17 had three, and 17 had five. In the other 50 cases (group B) the sutures were postplaced—one postplaced suture in 16 cases, three in 18 cases, and five in 16 cases. Pre- and postoperative keratometry and retinoscopy were done on two follow-up visits, one at about 20 days after operation and the other at six weeks after operation.

Physiological astigmatism was present preoperatively in 82 cases and was absent in 18. The astigmatism was inverse in 37 (45 per cent) cases, direct in 30 (37 per cent), and bioblique in 15 (18 per cent) (Fig 1). The average astigmatism was 1·19 dioptres. The axis was at 180 or 90 degrees in 38 cases (Fig. 2). The average radius of the lesser curvature was 7·92 mm and of the greater curvature 7·70 mm (range from 6·79 to 9·4 mm).

Postoperative results

ASTIGMATISM

At the first follow-up examination at 20 days, 51 cases showed inverse astigmatism and 49 direct astigmatism. The average astigmatism was 5·15 dioptres. The increase in the incidence of inverse astigmatism was only from 37 cases preoperatively to 51 postoperatively, whereas the increase in direct astigmatism was from 30 to 49 cases. Also out of the 18 cases with no preoperative astigmatism five showed inverse and 13 showed direct astigmatism.

At the second follow-up examination at six weeks 72 cases had inverse astigmatism and 25 had direct astigmatism. Three cases had no astigmatism. The average astigmatism was 2·49 dioptres. The axis of astigmatism was at exactly 90 or 180 degrees in 33 (34 per cent) cases at 20 days (Fig. 3) and in 40 cases at six weeks (Fig. 4).

The radius of the lesser curvature had increased on average by 0·59 mm at 20 days. Between then and six weeks it decreased by 0·51 mm, so that the increase at the final follow-up was 0·08 mm.

The radius of the greater curvature had decreased by 0·24 mm at 20 days. Between then and six weeks it had increased by 0·08 mm, so that the decrease at final follow-up was 0·16 mm (Fig. 5).

Thus there was a decrease or flattening of the lesser curvature and an increase or steepening of the greater curvature during the postoperative

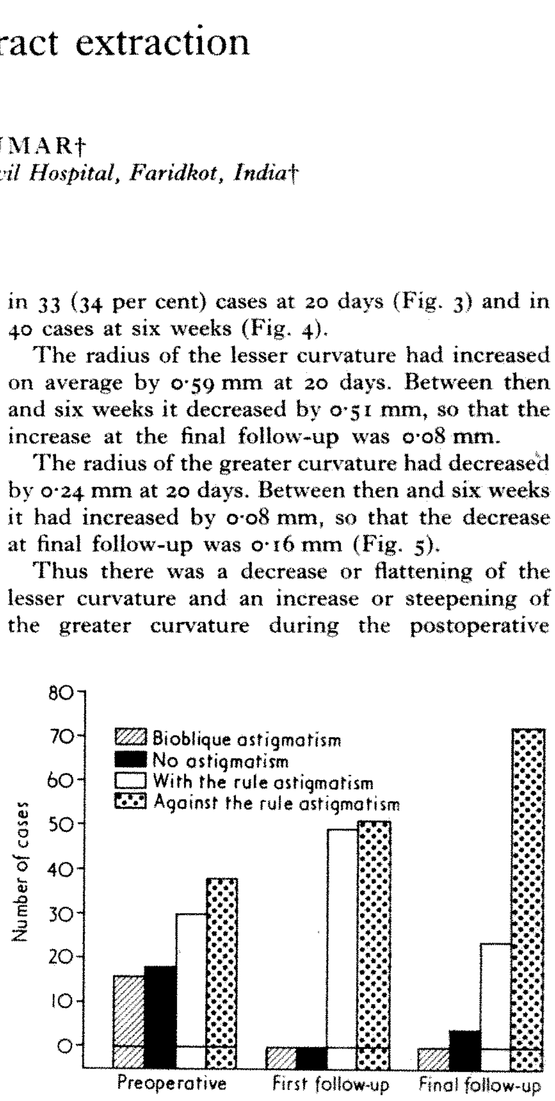

FIG. 1 *Type of astigmatism in* 100 *cases of cataract extraction*

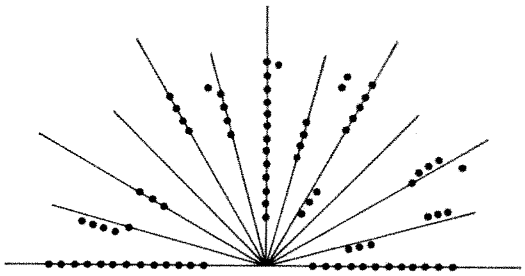

FIG. 2 *Distribution of axis of plus cylinder (corresponding to greater curvature) along different meridians in* 82 *cases of astigmatism (including bioblique astigmatism) before cataract extraction. Each dot represents one case*

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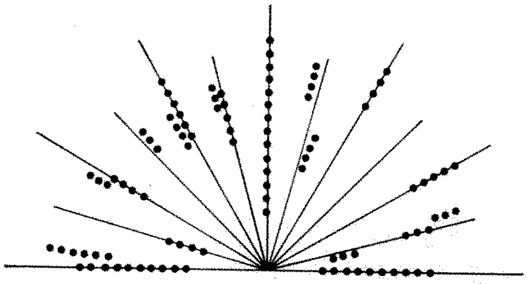

FIG. 3 *Distribution of axis of plus cylinder (corresponding to greater curvature) in different meridians in 100 cases of astigmatism 20 days after cataract extraction. Each dot represents one case*

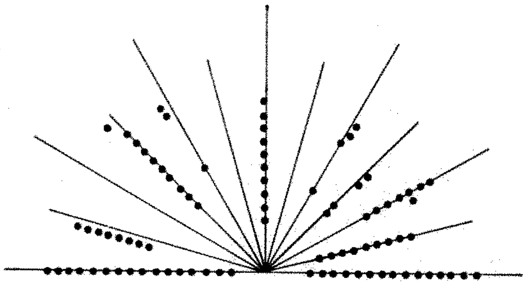

FIG. 4 *Distribution of axis of plus cylinder (corresponding to greater curvature) along different meridians in 97 cases of astigmatism 6 weeks after cataract extraction. Each dot represents one case*

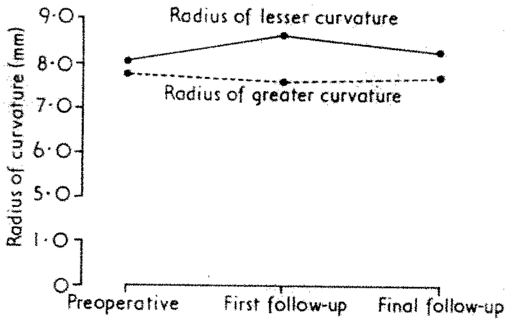

FIG. 5 *Mean changes in radii of curvatures*

Table *Comparison of pre- and postoperative astigmatism*

	No. of cases with direct astigmatism		*No. of cases with inverse astigmatism*	
	≤2D	*>2D*	*≤2D*	*>2D*
Preoperative	26	10	35	11
Postoperative	12	10	19	49

period. The flattening of the lesser curvature was relatively greater than the steepening of the greater curvature during the first 20 days, which accounted for the greater amount of astigmatism. At six weeks the changes were more in the greater curvature than in the lesser curvature. However, there was more variability in the changes in the lesser curvature than in those in the greater curvature. Also the changes that occurred from the first to the final follow-up were opposite to those that occurred from before operation to the first follow-up. Similar findings have been observed by Beasley (1967), whereas Lamba and Sood (1971) found the opposite.

In 44 cases the preoperative type of astigmatism did not change after operation. In 24 cases a preoperative direct astigmatism changed to inverse and in 13 cases an inverse changed to a direct. On the whole, the type of postoperative astigmatism tended to be the same as the preoperative (Table). This is in agreement with Floyd (1951).

TYPE AND NUMBER OF SUTURES

The amount of astigmatism associated with preplaced sutures (group A) was 4·37 D at 20 days and 2·53 D at six weeks, and that associated with postplaced sutures 5·93 D at 20 days and 2·45 D at six weeks (Fig. 6).

Analysis of the amount of astigmatism in groups A and B at 20 days in relation to the number of sutures was as follows: one suture, 5·02 D (group A) and 7·20 D (group B); three sutures, 3·33 D (group A) and 5·21 D (group B); five sutures, 4·79 D (group A) and 5·49 D (group B) (Fig. 7). Corresponding figures for the second follow-up at six

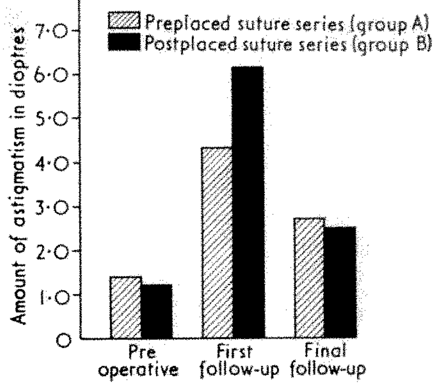

FIG. 6 *Amount of astigmatism related to type of suture*

weeks were as follows: 3·69 D and 3·49 D; 1·83 D and 1·80 D; 2·15 D and 2·13 D (Fig. 8).

The difference between the average amount of astigmatism at six weeks between pre- and post-placed sutures was insignificant. In both groups an increase in the number of sutures from one to three resulted in a significant decrease in astigmatism. Increasing the number of sutures from three to five did not result in any further decrease in astigmatism—on the contrary, there was a slight increase.

RETINOSCOPY

Retinoscopy at 20 days gave the following values: spherical +10·47 D; + cylinder on retinoscopy +2·99 D; cylinder on keratometry 5·15 D. The comparable values at six weeks were +11·00 D; +1·77 D; and 2·49 D, respectively. There was an increase of 0·53 D in the spherical and a decrease of 1·22 D in the cylindrical value from first to final follow-up. This is in agreement with Lamba and Sood (1971). There was no correlation between the amount and axis of cylinder as measured on retinoscopy and keratometry. This is supported by Fonesca Calderia (1961) and Beasley (1967).

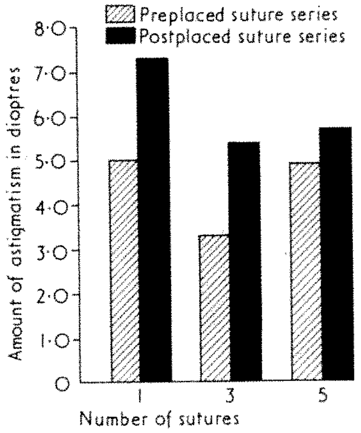

FIG. 7 *Distribution of amount of astigmatism between groups A and B at 20 days related to number of sutures*

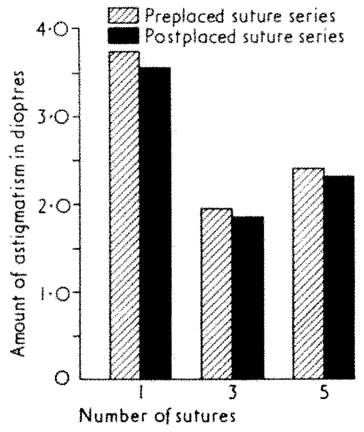

FIG. 8 *Distribution of amount of astigmatism between groups A and B at second follow-up (6 weeks) related to number of sutures*

STATISTICAL SIGNIFICANCE

There was no significant difference in the amount of postoperative astigmatism whether pre- or post-placed sutures were used. The decrease in the amount of astigmatism with three sutures was significant. The amount of astigmatism was slightly higher with five sutures than with three, but the difference was not significant.

Discussion

This study shows that the number but not the type (pre- or postplaced) of sutures used at cataract extraction affect the amount of postoperative astigmatism. Astigmatism was significantly less when three sutures rather than one were used. The amount of postoperative astigmatism with five sutures was slightly higher than with three sutures, but not significantly so. Three sutures are therefore the optimum number to use but it does not matter whether they are pre- or postplaced.

Our results in relation to the number of sutures are supported by Bengisu (1963), Müller (1965), McLean (1967), and Truhlsen (1968). Taylor (1959), however, preferred five radial and appositional sutures. Nirankari and Khanna (1968) agree with us that it is immaterial whether pre- or post-placed sutures are used in cataract wound closure, although Singh and Goel (1969) disagree.

The preoperative incidence of physiological astigmatism in our cases—82 per cent—is much higher than that reported by some others, as follows: 10·56 per cent (Mugge, 1908); 7·47 per cent (Luhl, 1909); 44·39 per cent (Cavara, 1922); 48·10 per cent (Leibowiez, 1928); 42 per cent (Nirankari and Khanna, 1968), 60 per cent (Kapoor, 1965), and 69 per cent (Singh and Goel, 1969). It is almost similar to the 75 per cent of Zamora (1904) and the 79 per cent of Beasley (1967) but less than the 95 per cent reported by Duke-Elder (1949).

Our average astigmatism of 1·19 D is higher than the 1·0 D quoted by Donders (1864), the 0·75 D by Pfalz (1885), the 1·04 D by Jackson (1932), the 0·75 to 0·5 D by Sørensen (1944), the 0·97 D by Kapoor (1965), the 0·75 D by Beasley

(1967), and the 0·5 to 0·75 D by Duke-Elder (1970). Our 38 cases with an axis of astigmatism at 180 or 90 degrees are fewer than those quoted by Singh and Goel (1969). The range of radius of curvature agrees with that found by Tron (1934, 1935).

The tendency for direct astigmatism to increase postoperatively, seen in our cases at first follow-up, may well be a sutural phenomenon, as first described by Floyd (1951) and later by Beasley (1967), and Elenius and Karo (1968). A contrary view has been expressed by Groenholm (1935), Nirankari and Khanna (1968), and Singh and Goel (1969). Our finding that the amount of postoperative astigmatism was unrelated to the preoperative amount accords with the findings of Beasley (1967).

We draw the following conclusions from our study.

1. Healing of the corneal wound after cataract extraction invariably produces an inverse type of astigmatism after six weeks.
2. Astigmatism immediately after operation is high compared with that after six weeks, when it is reduced to almost a half. At six weeks there is an overall decrease or flattening of the lesser curvature and an increase or steepening of the greater curvature.
3. On the whole, postoperative astigmatism tends to be of the same type as preoperatively, especially in cases with preoperatively inverse astigmatism. There is no correlation between the amount of preoperative and postoperative astigmatism.
4. There is no appreciable difference between the change in the amount of astigmatism with pre- or postplaced sutures. Therefore postplaced sutures are in no way inferior to preplaced.
5. The optimum number of sutures, whether pre- or postplaced, is three. Three sutures produce least astigmatism, multiple sutures are better than one, but an increase from three to five does not serve any purpose.
6. The changes observed on retinoscopy show a gradual increase in the spherical value and a decrease in the amount of cylinder up to six weeks. The value of the cylinder required is less than that observed on keratometry; the two bearing no relationship.

Summary

One hundred cases of uncomplicated cataract with clear corneae had cataract extraction and were examined at 20 days and six weeks after operation. Keratometry was done preoperatively and keratometry and retinoscopy at each of the follow-up visits. The study was undertaken to evaluate the type (whether pre- or postplaced) and the number of sutures (one, three, or five) that produce the least postoperative astigmatism. We found that the type of suture was immaterial but that three sutures produced the least astigmatism.

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Treatment of uniocular aphakia

A comparison of iris clip lenses with hard corneal contact lenses

S. P. B. PERCIVAL AND K. M. YOUSEF
From Scarborough Hospital, Scarborough

Since 1949 (Ridley, 1951) attempts have been made to correct uniocular aphakia by insertion of a lens intraocularly. Results from using angle-supported lenses have been uniformly poor, mainly because of damage to the corneal endothelium and to the trabecular mesh-work. Iris-supported lenses were used with success during the 1960s (Binkhorst and Leonard, 1967; Dallas, 1970). These lenses did not produce glaucoma but because of problems arising from lens dislocation and late corneal oedema most surgeons still preferred either to leave the uniocular cataract untouched or after extraction to substitute a contact lens.

It is well known that elderly patients are often intolerant of aphakic glasses and contact lenses, and Jaffe (1975a) stated that for patients over the age of 67 years intraocular lenses were more suitable. It is not disputed that the intraocular lens is often the treatment of choice in such an age group, but with improvements in microsurgical technique and design of the lens, the problems encountered in younger patients have been largely overcome and short-term visual results have been considerably improved. It is therefore the purpose of this paper to compare the results using intraocular lenses and hard corneal contact lenses in a predominantly presenile age group.

Material and methods

Twenty-five consecutive patients with uniocular pseudophakia aged between 55 and 75 years at the time of surgery (Group A) were matched as closely as possible for age and sex (Table I) with 25 patients who were offered a conventional hard contact lens trial for uniocular aphakia (Group B). Twenty of Group B were consecutive cases and the contact lens trial was offered postoperatively, two entered the trial between one and two years after surgery, and three entered more than two years after surgery. Criteria for entry were an absence of preoperative macular degeneration, glaucoma, high myopia, and diabetes mellitus, and they had to have a corrected visual acuity of 6/12 or better in the fellow eye. The mean age at the time of surgery for Group A was 66·3 years and at the time of entry for Group B, 67·5 years.

The standard cataract extraction was carried out under general anaesthesia using an *ab externo* microsurgical step incision, six or seven preplaced sutures, chymotrypsin, two peripheral iridectomies, intracapsular cryoextraction, and re-formation of the anterior chamber with Miochol. In addition in Group A a four-loop Binkhorst iris clip lens was inserted, the anterior superior loop being sutured to the iris midstroma with 10/0 Perlon. These patients also received subconjunctival Depomedrone and framycetin at the end of the operation, and the majority of those under the age of 70 years received preoperative intravenous mannitol and hyperventilation anaesthesia. Postoperatively betamethasone was begun on the fifth day and used for six to eight weeks in both groups and pilocarpine 2 per cent was instilled daily for at least six months in Group A.

Postoperative examination included slit-lamp assessment for uveitis and iris atrophy, applanation tonometry, visual acuity for near and distance, and assessment of binocularity using the Wirt stereotest. Macular oedema did not necessarily show an obvious fundus abnormality, but was confirmed by the presence of macular scotoma on the Amsler recording chart associated with falling visual acuity.

Results

Of 25 patients offered a conventional hard contact lens trial (Group B), 10 (aged between 67 and 74 years) declined chiefly because of apprehension about handling the lenses or losing them. Five other patients abandoned contact lenses after a few months because of difficulty in handling them or discomfort. There were 10 patients who were able to wear contact lenses for more than 10 hours a day but even so, two of these became erratic and abandoned them after 18 months to two years' wear.

Table I *Age and sex*

Age (years)	*Men* *A*	*B*	*Women* *A*	*B*
55–61	3	2	2	0
62–68	5	6	7	5
69–75	4	4	4	8
Mean	66	65	67	69

Address for reprints: S. P. B. Percival, FRCS, Consultant Ophthalmic Surgeon, Scarborough Hospital, Scarborough, North Yorkshire YO12 6LQ

Table II contrasts the disappointment of patients in Group B with the dramatic recovery of vision in Group A. Just three weeks after surgery most of those in Group A were able to see around 6/12 unaided. It will be seen that two years after the operation a patient not wearing glasses was nearly twice as likely to be seeing 6/9 or better in Group A than in Group B.

These satisfactory unaided visual results are related to a consistent lack of postoperative astigmatism possibly reflecting on the surgical technique, involving at least five preplaced sutures before the eye is opened. Postoperative astigmatism was 0·75 D or less compared to the fellow eye in 70 per cent (35 patients) of the whole group, and less than 1·5 D in 94 per cent. There were no patients requiring a postoperative cylindrical correction above 2·0 D.

A general feature of Group A was an improved depth of focus compared to the normal presbyopic eye. Thirteen patients (52 per cent) could read N8 unaided, eight of these could read N5 unaided, and four patients (16 per cent) could actually see both 6/9 and N5 unaided and did not require postoperative glasses.

Table III shows the best visual potential in the two groups when the patients were using glasses. In assessing acuity a slight adjustment was made for aphakic magnification in that for 6/5 to be recorded all the letters had to be correct for the patient wearing aphakic spectacles, but only the majority for the patient with pseudophakia or a contact lens. Better visual results again were obtained for Group A reflecting an absence of serious complications; at two years 93 per cent of them could see 6/9 or better. Patients in Group B were often disappointed because their operated eye had not been brought into use; of those in whom the vision of the fellow eye had dropped to 6/12 or worse because of progressing cataract only five out of 10 would wear an aphakic correction at one year, eight out of 10 at two years' postoperation.

Table II *Comparison of visual acuity between Group A unaided and Group B unaided or with contact lenses when worn. (Patients given as percentage of numbers followed-up for given period)*

	Period of follow-up									
	3 *weeks*		2 *months*		1 *year*		2 *years*		3 *years*	
Visual acuity	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
	25*	25*	25*	25*	25*	25*	14*	19*	4*	13*
< 6/60	4	100		100		60		63		92
6/60–6/24	24		20		20		7		25	
6/18–6/12	56		36		28		21		25	
6/9 or better	16		44		52	40	72	37	50	8

*Number of patients

Table III *Comparison of best visual acuity between Group A and Group B with additional spectacle correction. (Patients given as percentage of follow-up)*

Visual acuity	*Period of follow-up*							
	2 *months*		1 *year*		2 *years*		3 *years*	
	A	*B*	*A*	*B*	*A*	*B*	*A*	*B*
	25*	25*	25*	25*	14*	19*	4*	13*
6/24–6/12	4	12	8	12	7	11		8
6/9–6/6	52	64	60	64	53	63	25	77
6/5	44	24	32	24	40	26	75	15
No. not using aphakic correction		25*		13*		9*		9*

*Number of patients

Stereopsis

Using the Wirt stereotest 17 patients (68 per cent) in Group A regained full stereoscopic vision (to 40″ or 50″ of arc), and all in this group regained stereopsis to 140″ of arc or better. By contrast, in Group B only four of the 10 patients wearing contact lenses regained full stereoscopic vision, three others were stereoscopic to 100″ arc or better, and three were worse than 140″ arc. Girard, Friedman, Moore, Blan, Binkhorst, and Gobin (1962) also reported relatively poor stereopsis with conventional contact lenses (46 per cent stereopsis) compared with intraocular lenses (82 per cent stereopsis).

Diplopia was never a serious problem but was initially disconcerting for three of the contact lens wearers.

Eikonometry was performed using the Hawkswell eikonometer (Nolan and Hawkswell, 1974) on three of the patients wearing contact lenses. These gave an average reading of 1·8 per cent magnification. The same instrument was used on 10 patients from Group A and gave an average reading of 0·2 per cent magnification (range −1·7 to +1·9 per cent).

Complications

Complications (Table IV) were not serious and did not show any clear weighting for either group. The single case of corneal oedema was from an ill-fitting contact lens and was quickly reversed. The case of lens subluxation occurred 22 months after surgery in one of the two patients whose pupil sphincter failed to constrict in the immediate postoperative period. The pupil diameter was 4·5 mm at the time of subluxation and the reposition of loops was readily corrected by non-surgical means.

Table IV *Complications (50 patients)*

	Group A	*Group B*
Vitreous loss	1	1
Hyphaema	1	1
Iridocyclitis	2	2
Atonic pupil sphincter	2	1
Macular oedema	6	3
Corneal oedema	0	1
Subluxation of inferior loop	1	—

MACULAR OEDEMA

Some form of clinical macular oedema was noted in 24 per cent of Group A and in 12 per cent of Group B. Visual deterioration began some time between the second and fourteenth postoperative month and in four of Group A it lasted less than three months. Macular oedema may be presumed to have occurred in a larger number of Group B but either at a time when the aphakia was uncorrected or to patients who did not consider the defect to be of any greater significance than the other difficulties of corrected aphakia. Gills (1975) in a review of intraocular lenses found there was an incidence of about 20 per cent of macular oedema, and angiographic evidence of macular oedema is known to develop in 40 to 60 per cent of uncomplicated cataract extractions (Irvine, Bresky, Crowder, Forster, Hunter, and Kulvin, 1971; Toshioka and Kawashima, 1971; Hitchings, Chisholm, and Bird, 1975), but the mechanism is unknown. Jaffe (1975b) showed that the incidence of macular oedema is similar whether the intra- or extracapsular method of extraction is employed, and in the present series there was no correlation with vitreous traction (as suggested by Irvine, 1953) or with inflammation or vascular disease (as suggested by Gass and Norton, 1966). In only three patients did the visual loss extend to 6/24 or worse (two in Group B, one in Group A). The transient nature of macular oedema is well known (Gass and Norton, 1969; Jacobson and Dellaporta, 1974) and in this series the vision ultimately returned to 6/5 in some and to 6/12 or better in all patients.

Conclusions

A visual potential in Group A as good as or better than in Group B over a two- or three-year-period of follow-up suggests that in the age group under discussion an intraocular lens is justifiable for all patients with uncomplicated cataract and not merely those with uniocular cataract. In this series more than half the patients with intraocular lenses consistently saw 6/9 or better unaided, and more than 90 per cent saw 6/9 or better with spectacle correction.

Optical advantages of intraocular lenses compared with contact lenses are immediate restoration of sight, better visual acuity, better stereopsis, and an improved depth of focus for the patient.

Macular oedema occurred clinically in 24 per cent of the intraocular lens group and is more likely to produce symptoms than in patients without an implant. However, further research is required to prove that it is more severe than in other patients, and at present it should not be considered a serious complication since, although it may last several months, an eventual return of visual acuity of 6/9 or better may be anticipated.

Summary

The visual results, stereopsis, and complications have been assessed on 50 patients in a presenile age group treated for uniocular aphakia. Twenty-five patients received a Binkhorst four-loop lens implant at the time of cataract surgery and 25 were offered a conventional hard contact lens trial postoperatively. The period of follow-up ranged from one to three years.

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Internuclear ophthalmoplegia
An electro-oculographic study of peak angular saccadic velocities

A. C. BIRD* AND J. LEECH
From the MRC Hearing and Balance Unit, Institute of Neurology, National Hospital for Nervous Diseases, London

Internuclear ophthalmoplegia is a well-recognized disorder of horizontal eye movements, characterized by impairment of adduction (Holmes, 1921) and nystagmus of the abducting eye (Harris, 1944). Studies of human histopathology (Cogan, Kubic, and Smith, 1950; Christoff, Anderson, Nathanson, and Bender, 1960; Kupfer and Cogan, 1966) and animal experiments (Carpenter and McMasters, 1963; Carpenter and Strominger, 1965) show that it can be attributed to a lesion of the medial longitudinal fasciculus between the levels of the sixth and third nerve nuclei, on the side of the abnormally adducting eye. It has been inferred that the lesion affects axons arising from cells in the paramedian pontine reticular formation and passing to the medial rectus motor neurons in the oculomotor nerve (Bender and Weinstein, 1950; Carpenter and McMasters, 1963; Carpenter and Strominger, 1965; Fuchs and Luschei, 1970). However, recent anatomical studies have failed to demonstrate direct connexions between the paramedian pontine reticular formation and the ocular motor nuclei (Grabiel, 1975). In addition, the interneurons described by Baker and Highstein (1975) which relay from the sixth and third nuclei may be responsible for the mutual co-ordination of the two eyes during horizontal eye movements, and dysfunction of these neurons may be relevant to the pathogenesis of internuclear ophthalmoplegia.

The impairment of adduction is variable, the most severe lesions causing complete loss of adduction beyond the midline during contralateral gaze. In early reports, the clinical diagnosis depended on the recognition of a limited range of adduction. However, more recently it has been recognized that a less severe lesion may cause no apparent limitation in the excursion of the adducting eye, and the only clinical manifestation of the lesion may be reduced adduction velocity during horizontal saccades (Smith and David, 1964; Nelson and Engrov, 1969; Cogan, 1970; Bird and Sanders, 1970; Dell'Osso, Robinson, and Daroff, 1974; Metz, 1976). Identification of internuclear ophthalmoplegia may be further complicated by the coexistence of lesions involving the neural pathways controlling conjugate eye movements or the sixth nerve (Cogan, 1970).

In the early part of this century the characteristics of saccadic eye movements were defined (Dodge and Cline, 1901; Dodge, 1903) and the properties of saccades have been identified more precisely during the last two decades (Westheimer, 1954; Yarbus, 1956; Mackensen, 1958; Hyde, 1959; Rashbass, 1961; Robinson, 1964; Cook, Stark, and Zuber, 1966; Fricker, 1971; Ishikawa and Terakado, 1973; Boghen, Troost, Daroff, Dell'Osso, and Birkett, 1974). It has been shown that a saccade is the result of a pulse-step change in innervation in which there is intense innervation of the agonist muscle and disfacilitation of the antagonist (Miller, 1958; Tamler, Marg, Jampolsky, and Nawratzki, 1959). Contraction of the agonist muscle results from a train of high-frequency pulses in the ocular motor neurons, and even in small saccades the frequency approaches the maximum attainable in low threshold units. The size of the saccade is related to the number of excited neurons, the discharge rate of each neuron, and the length of the pulse of excitation. Saccades of over 20°, and those occurring away from the midline, cause near maximal innervation of all agonist motor neurons, and the characteristics of such eye movements are determined largely by the duration of excitation (Fuchs and Luschei, 1970; Robinson, 1970).

Peak velocity measurements have been used to characterize saccades. Such measurements may substantiate the clinical observation of slow saccades as a clinical sign of disease involving the neural mechanisms controlling eye movements (Gowers, 1879; Holmes, 1921; Starr, 1967). Reports have suggested the usefulness of these techniques in the detection of internuclear ophthalmoplegia (Bird and Sanders, 1970; Metz, 1976).

In this paper we report the results of quantitative assessment of peak angular velocities in a group of normal subjects and in a group of patients with a full range of ocular movements but with suspected

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*Also of Institute of Ophthalmology, Moorfields Eye Hospital, London

Address for reprints: A. C. Bird, FRCS, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

slow adduction on horizontal conjugate gaze indicating internuclear ophthalmoplegia. The measurements in the two groups were compared in order to prove the clinical sign, and to assess the incidence of associated subclinical ocular motor deficits.

Method

Eighteen patients with nervous system disease were chosen for study because internuclear ophthalmoplegia was suspected. Seventeen patients had multiple sclerosis and one (Patient 18) had a subarachnoid haemorrhage associated with clinical signs of brain stem dysfunction. Of the patients with multiple sclerosis, the history of disease varied from two months to 10 years and nine had no symptoms referrable to the visual system. In all patients adduction appeared to be slower than abduction during horizontal saccades, although in all but two cases (Cases 6, 16) adduction appeared full, and in all it was more than 30° beyond the midline. Twenty-five normal people were used as a comparison group. All normal subjects and patients studied had a visual acuity of 6/6, and none had used sedatives, hypnotics, or anticonvulsants during the week before testing.

All subjects were placed in a dental chair with a chin rest for stabilization. Ocular saccades of each eye were recorded by electro-oculography using electrodes over the medial and lateral canthi bilaterally, and an indifferent electrode was placed centrally over the nasion. The electrodes were a modification of those described by Hallpike, Hood, and Trinder (1960). A DC amplifier was used (Elema Schonander universal amplifier EMT 12) in conjunction with a linear ink jet writer (Elema Schonander minograf '61'). This amplifier/recorder combination gave a linear frequency response up to 500 Hz falling off to 70 per cent amplitude at 650 Hz. Peak velocities were assessed by measuring graphically the steepest part of the record during the ocular deviation.

Fixation targets were tungsten filament bulbs viewed through a 2 mm aperture on a black background. The central target was 60 cm in front of the corneae, and two further targets were set at a visual angle of 30° to either side of the central target. After calibration, the targets were illuminated one at a time and the subject was asked to look carefully at the light. Only 30° movements were asked for—that is, centre to left, left to centre, centre to right, right to centre. The test was continued until at least five accurate saccades had been recorded in each of these directions. Calibration was repeated at intervals during the test. Individual peak velocity values were used to calculate mean velocity and the 95 per cent confidence limits for each movement. Individual values were used to compare the results in patients with those in the normal group using Student's *t* test.

Results

The mean peak saccadic velocities and 95 per cent confidence limits for the normal group are shown in Table I. Four of the 200 mean individual values obtained were above the confidence limits and none was below. Student's *t* test was used to compare adduction and abduction velocities of each of the four saccades, and adduction was significantly faster in each case ($P<0{\cdot}001$). A similar comparison showed that centring was faster than decentring ($P<0{\cdot}001$).

The mean peak velocities of eye movements in the group with internuclear ophthalmoplegia are shown in Table I, and of each patient in Table II. Adduction and abduction peak velocities were compared and abduction was significantly the faster ($P<0{\cdot}001$), and in this respect the group differed from the normal subjects ($P<0{\cdot}001$). Adduction was slower than abduction bilaterally in all patients. A discriminant analysis was made on each patient and normal subject and everyone was correctly identified as belonging to the appropriate group.

The wave-form of the adducting eye described during saccades differed from normal but varied from one patient to another. In some the movement was slow but the symmetry was unaltered (Fig. 1*a*), while in others there was progressive fall-off of angular velocity as the saccade progressed (Fig. 1*b, c*).

Table I *Mean of peak eye velocities and* 95 *per cent confidence limits (in parentheses) during* 30° *horizontal saccades of* 25 *normal subjects and* 18 *patients with internuclear ophthalmoplegia (INO)*

	Right gaze				*Left gaze*			
Group	*Left to straight ahead**		*Straight ahead to right**		*Right to straight ahead**		*Straight ahead to left**	
	Right eye	*Left eye*	*Right eye*	*Left eye*	*Right eye*	*Left eye*	*Right eye*	*Left eye*
Normal	464 (584–343)	506 (634–379)	453 (582–324)	504 (627–381)	531 (660–402)	510 (642–347)	529 (669–389)	470 (601–340)
INO	323 (551–94)	231 (397–66)	298 (520–75)	162 (340–0)	202 (370–34)	317 (521–113)	157 (341–0)	309 (480–138)

* = 30° saccade

Table II *Mean of peak eye velocities during 30° saccades of each patient with internuclear ophthalmoplegia. The first 17 patients had multiple sclerosis and the last had suffered a subarachnoid haemorrhage with signs of brain stem dysfunction*

Patient	Length of disease (years)	*Right gaze*				*Left gaze*			
		*Left to straight ahead**		*Straight ahead to right**		*Right to straight ahead**		*Straight ahead to left**	
		Right eye	*Left eye*	*Right eye*	*Left eye*	*Right eye*	*Left eye*	*Right eye*	*Left eye*
1	3	340	310	326	208	218	338	40	328
2	4	212	232	158	96	185	432	126	338
3	3	354	267	294	240	151	313	143	233
4	2/12	581	365	510	330	438	445	327	441
5	5	400	242	363	227	339	418	295	358
6	5	218	185	185	39	133	175	97	193
7	6	187	148	221	98	130	217	99	188
8	1	410	275	392	213	178	470	136	357
9	3	353	285	234	181	308	387	293	365
10	6	333	143	315	125	97	284	77	301
11	6/12	166	165	227	115	130	153	100	212
12	4	379	277	342	247	200	333	140	378
13	1½	302	265	260	218	235	288	159	306
14	2	532	103	383	271	137	393	99	429
15	10	399	218	383	128	224	445	197	507
16	7	217	186	167	40	167	169	89	188
17	2	587	161	430	129	198	260	166	316
18		175	190	226	97	218	194	129	298

* = 30° saccade

Occasionally two distinct fast phases were recorded within the saccade (Fig. 1*b*, *c*). In each patient the wave-form was reproduced consistently for a particular saccade, although adduction in one direction often differed from adduction in the other.

The group of patients with internuclear ophthalmoplegia had significantly slower abduction than the normal subjects in all saccadic movements ($P < 0{\cdot}001$). In eight, abduction peak velocities of both eyes were below the 95 per cent confidence limit calculated from the normal group, and in a further three abduction was slow in one eye. In a majority abduction slowing was more pronounced during the decentring than the centring movement.

Discussion

It was established recently that ocular peak angular velocity is higher during large saccades than small, although the relationship is not linear and reaches its greatest at about 25° (Hyde, 1959; Cook, Stark, and Zuber, 1966; Boghen and others, 1974). There is some variation in the findings concerning normal peak velocities and the relative peak velocities of different eye movements. Average peak velocities during 30° saccades measured in a series of normal subjects have been variously reported as 580° per second (Westheimer, 1954); 529° per second (Hyde, 1959); 452° per second (Ishikawa and Terakado, 1973), and 428° per second (Boghen and others, 1974). Speeds of over 600° per second have been recorded and Boghen and others (1974) consider 200° per second as the lower limit of normal. It has been reported that temporal saccades are faster than nasal saccades (Robinson, 1964; Fricker, 1971) and that they are equal in both directions (Hyde, 1959); that adduction saccades are faster than abduction saccades during large eye movements (Boghen and others, 1974) and that they are equal in small saccades (Boghen and others, 1974). It has also been reported that centring movements with respect to the primary position are faster than decentring (Hyde, 1959; Cook and others, 1966). The variability of results may be related to some extent to the different experimental techniques used. The stimuli used include alternating fixed and moving targets, and the recording systems include high-speed photography, corneal and contact lens reflexion, AC and DC electro-oculography, contact lens scleral search coil in a magnetic field, and infrared reflection. In some studies the measurements were restricted to accurate eye movements only, while in others no such restriction was made. The limited data are another likely source of discrepancy; in many studies few subjects were used and few movements analysed.

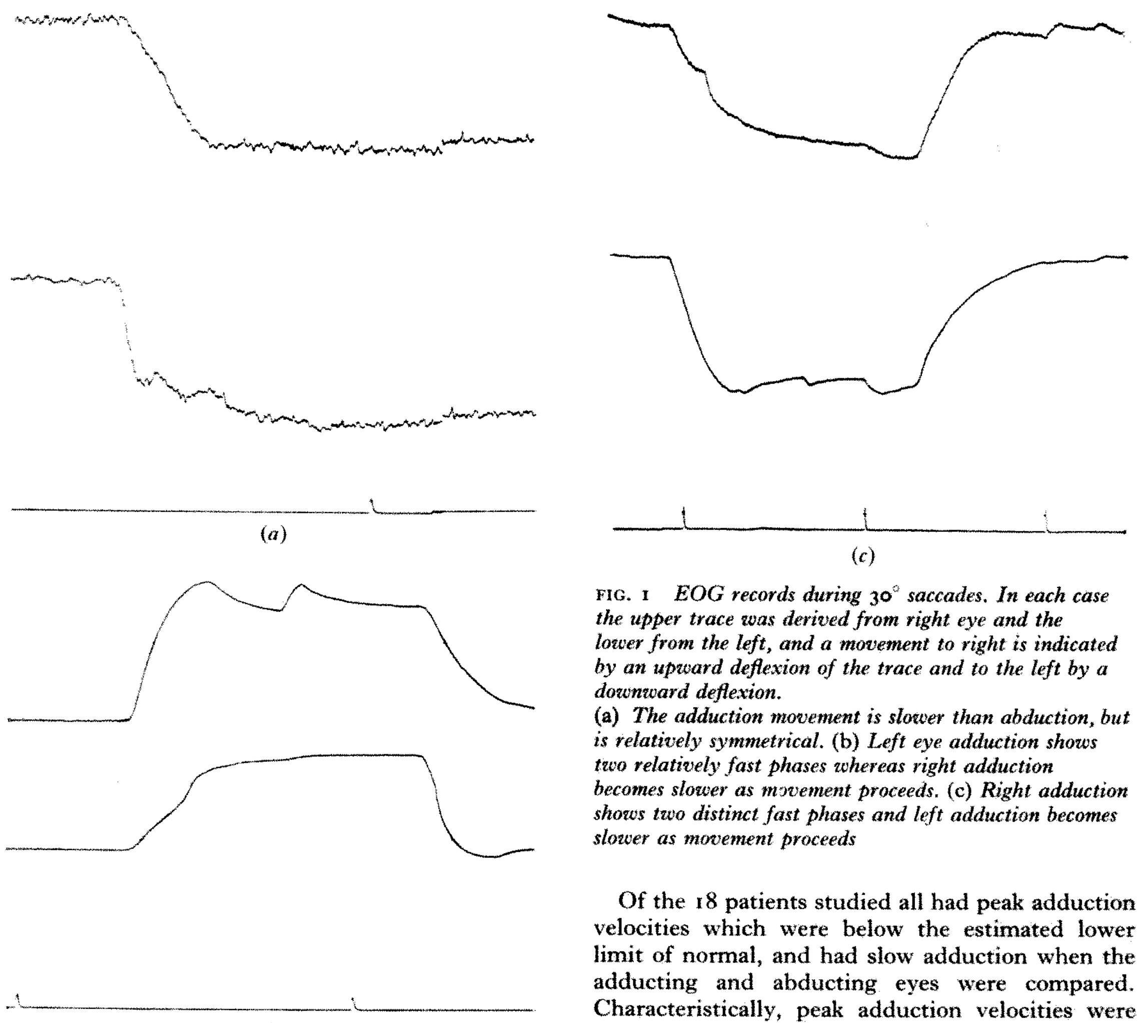

FIG. 1 *EOG records during 30° saccades. In each case the upper trace was derived from right eye and the lower from the left, and a movement to right is indicated by an upward deflexion of the trace and to the left by a downward deflexion.*
(a) *The adduction movement is slower than abduction, but is relatively symmetrical.* (b) *Left eye adduction shows two relatively fast phases whereas right adduction becomes slower as movement proceeds.* (c) *Right adduction shows two distinct fast phases and left adduction becomes slower as movement proceeds*

This is important, since it has been shown that there is considerable intersubject variation in peak velocities for the same movements and that the speed may vary in the same subject (Boghen and others, 1974). Therefore, there appear to be no accepted data for peak velocities during saccades at present, and as Boghen and others (1974) emphasized, normal values have to be established by each laboratory.

That the average peak adduction velocity in the 25 normal subjects in this series was significantly faster than the abduction velocity is in complete agreement with the findings of Boghen and others (1974). Adduction was consistently faster than abduction in 22 of the 25 subjects during all eye movements measured. The speeds are somewhat faster than those recently published but there was considerable inter- and intrasubject variability.

Of the 18 patients studied all had peak adduction velocities which were below the estimated lower limit of normal, and had slow adduction when the adducting and abducting eyes were compared. Characteristically, peak adduction velocities were relatively slower during the movement away from the midline and towards the limit of adduction, than during movement towards the midline, and in three a relative slow movement was detected only during the decentring movement. It can be concluded that measurement of peak velocities is useful in detecting internuclear ophthalmoplegia, or confirming the presence of suspected slow adduction. In this way the procedure may be critical in demonstrating unequivocally the presence of a second lesion in the central nervous system when a patient with restricted central nervous system deficit, such as optic neuritis or spastic paraplegia, is suspected of having multiple sclerosis.

It appears that slow saccades rather than limited saccades are characteristic of mild 'internuclear ophthalmoplegia' due to primary intrinsic demyelination. It has been established that, in its most severe form, demyelination causes a block in axonal conduction (McDonald and Sears, 1970). Such a lesion in the internuclear pathways would be expected to cause limitation of the range of adduction during horizontal saccades.

However, milder lesions render the axon incapable of conducting high-frequency signals and cause delay in conduction of impulses by the axon (McDonald and Sears, 1970). The ocular motor nerves are characterized by the high frequency of nerve impulses (Robinson, 1970); if the central ocular motor system is similar in this regard an element of nerve block may be induced by demyelination. Such an alteration in conduction would cause the movement to be hypometric and slow, but occupy normal time. It is likely that the impulse frequency required to maintain the eyes in the eccentric position would be less affected so that after the initial saccadic movement the adducting eye would drift slowly on to target (Robinson, 1971). That such a wave-form was recorded (Fig. 1*b*, *c*) suggests that an element of conduction block of high-frequency impulses plays a part in producing disordered adduction in internuclear ophthalmoplegia. Unequal slowing of conduction of internuclear fibres in the medial longitudinal fasciculus would lengthen the overall pulse of excitation generating the saccade and reduce its peak frequency. This might account for slow movement with symmetrical wave-form (Fig. 1*a*). It is somewhat more difficult to account for the two distinct fast phases which were recorded during the single adduction movement (Fig. 1*b*, *c*). It is unlikely that these two movements were formulated separately by the brain stem oculomotor generators since uniocular and vergence movements are characteristically slow (Weber and Daroff, 1971). Such a movement would occur if a lesion caused delayed conduction in some of the nerve fibres connecting the saccadic generator with the medial rectus motor pool leaving others intact. This would result in two pulses of adduction excitation at the oculomotor nerve and the interval between the two would correspond to the relative delay in one fibre population compared with the other.

The results also show that abduction speeds in these patients with internuclear ophthalmoplegia were slow. Slowing of abduction may be due to lack of inhibition of the medial rectus muscle antagonizing the movement (Loeffler, Hoyt, and Slatt, 1966). However, no clinical correlation of this lack of inhibition has yet been shown and we have not demonstrated any correlation between the severity of the internuclear ophthalmoplegia and abduction slowing. Therefore, there is no evidence that slow abduction is an integral part of the internuclear ophthalmoplegia. Slow abduction may have been caused by concurrent lateral rectus paresis due to lesions affecting the sixth nerve or the connexions between the pontine reticular formation and the sixth nerve nucleus, as proposed by Rothstein and Alvord (1971). Slowing of eye movements has been described in patients with lateral rectus paresis (Metz, Scott, O'Meara, and Stewart, 1970) but not in the absence of restricted movement.

Alternatively, slow abduction in these patients with internuclear ophthalmoplegia may be due to a lesion of the supranuclear mechanisms governing horizontal saccades, although no patients had a previously recognized horizontal gaze paresis. Reduction of saccadic peak velocity has been recognized as a manifestation of horizontal gaze paresis even in the presence of a full range of ocular movements (Gowers, 1879; Holmes, 1921; Starr, 1967). The occurrence of horizontal gaze paresis in patients with internuclear ophthalmoplegia has been emphasized in the past (Cogan, 1970) but the frequency of this association has not yet been established. In this series of patients with internuclear ophthalmoplegia, this feature occurred in as many as 11 out of a total of 18, and was unilateral in three and bilateral in eight. Normal abduction velocities in the remaining five patients do not necessarily indicate the integrity of the supranuclear gaze mechanisms since in four the peak velocities were close to the 95 per cent confidence limit, and the incidence of supranuclear lesions may be even higher than indicated by these figures. Gaze paresis and the internuclear ophthalmoplegia may be due to the same lesion (Fisher, 1967), but it is equally possible that more than one lesion caused the multiple ocular motor deficits in these patients. All patients studied had disease which was multifocal in nature, and all had clinical evidence of more than one lesion; it is relevant that four of the five with normal abduction velocities had a short history of the disease.

The high frequency of gaze paresis may be relevant to the nystagmus which is so characteristic of internuclear ophthalmoplegia. The nystagmus is usually attributed to the abducting eye only, but in most patients nystagmus can be detected in the adducting eye also (Fig. 1*b*); the nystagmus is less in the adducting eye so that it is asymmetrical rather than unilateral. The nystagmus on extremes of horizontal gaze may be due to gaze paresis, the low frequency and irregularity of the nystagmus being characteristic of gaze paretic nystagmus (Jung and Kornhuber, 1964). Asymmetry of eye movements is well recognized during optokinetic nystagmus (Smith and David, 1964) and post-rotational nystagmus (Sjroky, Kieicova, and Ymazah, 1973), and has been attributed to the small excursion of slow adduction saccades and superadded convergence tone (Dell'Osso and others, 1974). Similarly the asymmetry of the nystagmus on lateral gaze could be attributed to the internuclear ophthalmoplegia. It has been shown in many of our patients that adduction saccades become slower as the eye nears full adduction, and this would certainly account for the high degree of asymmetry of the nystagmus on extreme lateral gaze, and the difficulty in detecting the movement of the adducting eye.

Summary

Peak angular saccadic velocities were measured during 30° saccades in 18 patients with internuclear ophthalmoplegia who had full or nearly full adduction range, and 25 normal subjects. The following observations were made:

1. In the normal group adduction velocities were significantly faster than abduction velocities and centring movements were faster than decentring movements.
2. In patients with internuclear ophthalmoplegia adduction movements were significantly slower than in normal subjects and were significantly slower than abduction velocities.
3. Abduction velocities in patients with internuclear ophthalmoplegia were significantly slower than abduction velocities in normal subjects.

It was concluded that measurements of peak angular velocities during saccades may be useful in detecting internuclear ophthalmoplegia or confirming the presence of suspected internuclear ophthalmoplegia. Slow abduction suggests that many patients with internuclear ophthalmoplegia (60 per cent in this series) have lesions affecting the supranuclear pathways subserving horizontal conjugate gaze.

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A study of head and eye movement in spasmus nutans

M. GRESTY AND J. LEECH
From the MRC Hearing and Balance Unit, Institute of Neurology, National Hospital for Nervous Diseases, London

M. SANDERS AND H. EGGARS
From the Neuro-ophthalmology Department, National Hospital for Nervous Diseases, London

Spasmus nutans was first described by Raudnitz (1897) and although it is a rare clinical entity, it has been systematically documented by several authors (Cox, 1936; Norton and Cogan, 1954; Østerberg, 1937; Walsh, 1947; Wybar, 1971) all of whom have provided a characteristic clinical picture. All investigations of spasmus nutans have concluded that there is no relationship between the nystagmus and the head nodding because of the different frequencies involved. However, there are no reports in the literature of objective measurements of head and eye movements. Modern kinesiological recording methods are simple to perform and suitable for the recording of head movements. In addition recent studies of the normal patterns of head and eye co-ordination in man have helped in understanding the mechanisms involved (Mowrer, 1932; Hodgson and Lord, 1954; Crawford, 1960; Bartz, 1966; Fleming, Vossius, Bowman, and Johnson, 1969; Gresty, 1973, 1974).

The interrelationship of head and eye movements was recorded in a case of spasmus nutans using electro-oculographic techniques in conjunction with an optical method of recording head movements.

Case history

A 4-year-old-boy from Kuwait was referred for neuro-ophthalmological investigations.

At the age of 8½ months the parents had noticed rapid oscillatory eye movements. On beginning to walk they noted intermittent head nodding. This was marked initially but during the past year had improved. There was no history of neurological disorders and the family history was normal.

On examination there were intermittent episodes of horizontal and vertical oscillatory movements of small amplitude. They could be more marked in one eye or the other but seemed more marked in the abducting eye. On attempting convergence there was marked oscillation in the right eye. Ocular examination was otherwise normal with visual acuity of 6/5 in each eye and normal fundus examination.

EXPERIMENTAL METHOD

The patient was seated in a chair in an upright position which did not obstruct freedom of head movements. He was fitted with a light, unobtrusive spectacle frame that carried sockets and leads for DC electro-oculographic (EOG) recording of the horizontal movements of the left and right eye. The ear pieces of the frame were linked around the back of the head with an elastic band, which supported a small (1 W) non-directional infrared emitter on the occipit.

A Schottky barrier (United Detector Technology SC/25) linear motion photo detector was mounted with its sensitive surface in the focal plane of a 35 mm camera. The axes of the detector were orientated horizontally and vertically. The camera was placed to view the back of the patient's head. As the patient moved his head the detector gave *x*, *y* co-ordinate readouts of the linear motion of the infrared source which were sinusoidally related to the head rotation. Since the head-nodding consisted of small amplitude oscillatory rotations in the horizontal plane the *x* axis of the detector provided a signal which was approximately a linear function of head displacement. The patient was examined experimentally for two 1½-hour periods while continuous recordings were taken. Emphasis was laid on determining the specific stimuli which evoked the nystagmus and head movement and their interrelationships.

Results and discussion

Detailed characteristics of the head nodding and ocular movements which could not be determined by inspection were clarified by the recordings. The nystagmus consisted of a high-frequency (11 Hz) sinusoidal, convergence movement of both eyes (Fig. 2, upper traces). The peak to peak amplitude of oscillation was about 2°. During these oscillations some jerk-type nystagmus to the left occasionally occurred (Fig. 1, eye movements with stationary head). The head nodding consisted of a 3-Hz sinusoidal horizontal oscillation of the head with a peak to peak amplitude of about 3° (Fig. 2, lower traces). During the head nodding, perfectly

Address for reprints: M. D. Sanders, FRCS, Neuro-ophthalmology Department, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG

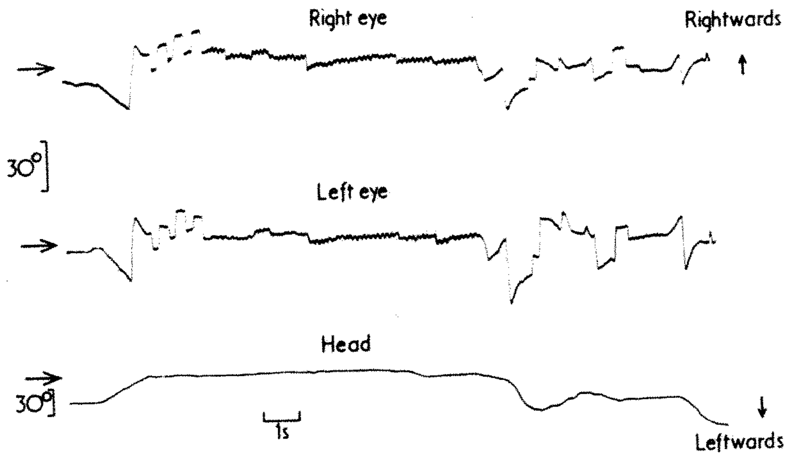

FIG. 1 *Displacements in horizontal plane of head and eyes recorded in a case of spasmus nutans. Horizontal arrows indicate primary gaze and primary head position. High frequency eye movements present during periods of quiescent head movement represent nystagmus of spasmus nutans*

normal compensatory eye movements were present (Fig. 2, lower traces).

Further examination of the head and eye movement recordings revealed consistently reproducible features which, to our knowledge, have not hitherto been reported and would appear to have important implications for understanding the nature of the disorder.

Of utmost importance is the consistent finding that the head nodding (Fig. 2, lower traces) always abolished the eye movements (Fig. 2, upper traces). The nodding was specifically elicited by novel stimuli (the most powerful being an unknown face) to which intense attention was paid. Hence it would appear that the head nodding is a mechanism which permits the discrimination of the finer features of a visual stimulus. In place of the abolished pathological nystagmus the eyes perform purely compensatory movements which aid vision during head displacements (Benson and Guedry, 1971). The frequency of the head nodding is well within the range of principal natural frequency components of voluntary head movements in humans (1 to 4 Hz). The tentative hypothesis may be made that the head nodding is *not* pathological in origin but may be considered to be an operant-conditioned response which, because of its powerful ability to supress the pathological nystagmus, is an adaptive behavioural pattern.

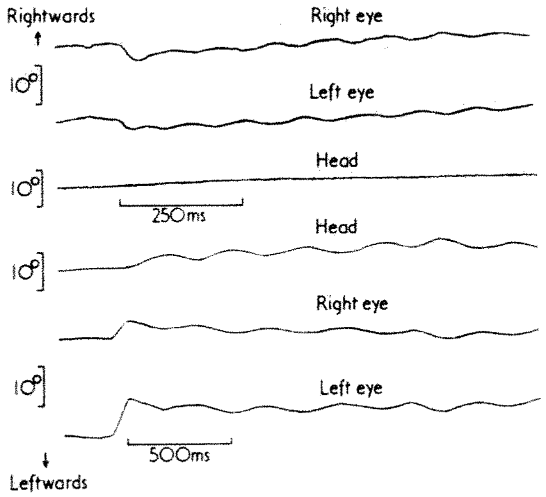

FIG. 2 *Displacement in the horizontal plane of the head and eyes in a case of spasmus nutans. Upper traces; head stationary, eyes executing pathological convergence oscillation. Lower traces; head nodding, eyes executing normal compensatory movements of vestibular origin*

There is some evidence against the hypothesis. Case histories are divided between those in which the parents report that head nodding had an earlier onset than eye nystagmus and those reporting the inverse sequence.

The nystagmus is abolished not only by head nodding but also by any head movements of significant amplitude (Fig. 1, later portions of the head movement trace). Isolated head movements of small amplitude (2° to 3°) did not necessarily abolish the nystagmus. It may be the case that in small children there is no requirement for prolonged periods of visual fixation so that any amplitude and frequency of head movement can be employed to abolish the nystagmus. In older children, such as the patient described here, prolonged fixation is required and as a consequence the suppressive head nodding becomes more refined. This consideration may explain the variety of movements reported in spasmus nutans. The small amplitude and high frequency of the refined head nodding produces, as in normal subjects, a purely compensatory eye movement (Benson, 1969).

The origin of the nystagmus is more in doubt than that of nodding. The nystagmus has a basic high-frequency component similar to the principal frequency components of saccadic eye movements (Barnes, 1973); therefore it is possible that the origin lies entirely in an imbalance of the saccadic pulse generating mechanism. It is envisaged that each eye is supplied with a high frequency train of saccadic pulses, alternately adducting and abducting the globe and producing an overall plant response in the form of sinusoidal oscillation.

Conclusions

The tentative hypothesis is made that head nodding in spasmus nutans is an operant-conditioned phenomenon which, by suppressing the pathological, high-frequency nystagmus aids visual acuity. It is not pathological *per se* but epiphenomenal. The eye nystagmus appears to be a disorder of the saccadic pulse generating mechanism(s). These conclusions were drawn from intensive observation of a single case of spasmus nutans. More information about the developmental history and patterns of motor co-ordination is needed before valid generalizations may be made but the low incidence of spasmus nutans impedes the satisfaction of this requirement.

Summary

A case of spasmus nutans was studied using objective recordings of head and eye displacement in order to generate a precise description of the ocular oscillations and head nodding and to investigate their interrelationships. The ocular-oscillations consisted of 11-Hz sinusoidal convergence movements. The head nodding consisted of a 3-Hz, 3° peak to peak, sinusoidal oscillation in the horizontal plane. The occurrence of the nodding always abolished the ocular oscillation which was replaced by normal compensatory eye movements which assisted visual acuity. The hypothesis is made that the head nodding is not pathological; it is a learned behavioural pattern which permits the patient to nullify the pathological eye movements. In order to test this hypothesis further, objective evidence is required to determine the precise order of appearance of the abnormal head and eye movements in spasmus nutans.

We wish to thank Dr K. J. Zilkha for allowing us to study and publish his case.

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Incidence of retinoblastoma in the Bantu of South Africa

JEFFREY FREEDMAN AND LEON GOLDBERG
From the Department of Ophthalmology, University of the Witwatersrand and Baragwanath Hospital, Johannesburg

There is no report on the incidence of retinoblastoma in the Bantu of South Africa. The incidence of any disease entity in a population often lends a clue to its aetiology and this forms an important part in the epidemiological study of the disease entity. This also applies to the study of neoplastic conditions and, as regards this report, to retinoblastoma in particular. The patients reported in this study all came from the Johannesburg area of South Africa and were seen mainly at the St John Eye Hospital, Baragwanath, during the 20-year-period from 1955 to 1976.

Clinical study

The patients were classified according to age, sex, and uniocular or binocular involvement.

Results

During the 20-year-period a total of 78 new cases of retinoblastoma were seen. This represents an average of just under four new cases each year. The birth rate derived from hospital clinic and census figures in the area from which the cases came is 40 000 live births a year. The incidence of retinoblastoma in the Bantu from this area is one per 10 000 live births.

The age and sex distribution of retinoblastoma were calculated for 71 patients (Table), but the ages of the remaining seven patients were unobtainable.

Nearly half of the children with retinoblastoma were in the two- to three-year age groups, while an equal number of children appeared in both the one- to two- and four-year age groups. Of the total number of patients (78), 64 had one eye involved and 14 had both eyes involved. The average age of the binocular cases at presentation was three years, and for the uniocular cases at presentation it was 3½ years. The ratio of boys to girls in the uniocular cases was 1·2 : 1 and in the binocular cases 3 : 1. In this series the ages of presentation were known in 71 cases. Of these, 80 per cent were diagnosed before the age of four years. The tumour had spread in 45 out of the 78 cases; in these it was poorly differentiated and had spread either well into the optic nerve, the orbit, the brain, or to bone. Only 13 per cent of these cases were binocular.

Address for reprints: J. Freedman, FRCS, Department of Ophthalmology, University of the Witwatersrand and Baragwanath Hospital, Johannesburg, South Africa

Table *Age and sex distribution of 71 patients*

Age (years)	*Males*	*Females*
1	1	1
1–2	9	6
2–3	15	14
3–4	6	4
4	9	6
Total	40	31

Discussion

In this series 80 per cent of cases were diagnosed before the age of four years. This corresponds with the findings of Taktikos (1966), and Tarkkanen and Tuovinen (1971). The series in the Bantu showed a moderate preponderance of males. This corresponds with the findings of Bech and Jensen (1961), Carbajal (1958), and Herm and Heath (1956). Tarkkanen and Tuovinen (1971) in their series demonstrated a slight preponderance of females (91 out of 171). The sexual incidence in the Bantu would therefore seem to coincide well with the incidence found in other series dealing mainly with Caucasoid populations. In a series (Sevel, Sealy, and Lawton, 1973) reported from Groote Schuur Hospital, South Africa, the sex ratio was similar to that of our series—that is, 40 males and 31 females—however, their race was not mentioned, but the comparison seems to imply that the numbers of patients seen in the Transvaal area are similar to those seen in the Cape area during a 20-year-period.

In our series 82 per cent had uniocular involvement and 18 per cent binocular. In other reported series, dealing mainly with Caucasoid populations, bilateral involvement varied from 30 to 50 per cent—for example, Carbajal (1958) 30 per cent, Jensen (1965) 30 per cent, Lommatzsch (1966) 59 per cent. Bilateral involvement was observed in 19·3 per cent of the 1760 cases on file in the Registry of Ophthalmic Pathology (Zimmerman, 1969). Thus it seems that binocular involvement in the Bantu is at the lower end of the scale of reported binocular incidence of the tumour. In a recent report dealing with 61 cases of retinoblastoma (Devesa, 1975), 50 were uniocular with a slight female preponderance.

In this series, 65 per cent of the uniocular cases showed that the tumour had spread resulting in a poor survival rate. There appeared to be a direct relationship between the time of presentation and the histology of the tumour, late presentation being associated with more advanced anaplastic appearance of the tumour. Herm and Heath (1956) suggest that the longer the tumours are present before presentation the less differentiated they seem to be histologically. Carbajal (1958) showed that the fatality rate was less when the duration of symptoms before treatment was two weeks to six months than when duration was more prolonged.

These observations seem to apply to this series in the Bantu and the anaplastic appearance in most of the Bantu cases was due to the longer existence of the tumour before presentation. Tumours seen in the Bantu at a relatively early stage showed the presence of typical rosettes, thus the retinoblastomas do not appear to be more aggressive in the Bantu. No family history was obtained in any of the patients in this series, unlike other reported series in which family history varied from 11 to 44 per cent (Carbajal, 1958; Pieroni, Lashmet, and Helveston, 1969).

Conclusions

It would seem from this study that the incidence per live birth of retinoblastoma in the Bantu is higher than that reported in series dealing with Caucasoids or series not specifying race.

The sexual difference is not significantly marked but there is a slight preponderance of males in the Bantu.

The average age of presentation of 3 to 3½ years corresponds well with that reported in other series.

The severity of the tumour in the Bantu appears to be because of late presentation of the patient to the hospital.

No family history was obtainable in any of the 78 cases.

Thus retinoblastoma in the Bantu is not an infrequently occurring tumour as has been reported, but is, in fact, more common than retinoblastoma reported in other series. Apart from the incidence, the pathological behaviour of the tumour in Bantus is very similar to that of retinoblastoma reported in other series most of which are predominantly in Caucasoid populations.

We wish to thank the Medical Superintendent of the Baragwanath Hospital for permission to publish this paper.

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Lactate dehydrogenase isoenzyme pattern in the eye muscles
Deviation in myopia

I. L. KAHÁN AND K. JUHÁSZ
From the Department of Ophthalmology, University Medical School, Szeged

Striated skeletal muscles consist of varying proportions of red and white fibres. These serve different functions according to their metabolic characteristics. Tonic contractions are mainly the function of the red muscle fibres, and rapid twitch movements that of the white. Their type of metabolism may be defined in terms of their lactate dehydrogenase (LDH) isoenzyme pattern. LDH isoenzymes in red muscle consist mainly of heart (H) type subunits, leading to aerobic metabolic paths, whereas those in white muscle are mostly of the muscle (M) type favouring only anaerobic routes.

Materials and methods

The LDH isoenzyme pattern in 46 extraocular muscle samples was determined. The samples were removed during surgery for squint on 40 otherwise healthy patients aged 6 to 15 years. The samples were grouped according to the refraction of the associated eye, the eye muscle from which they were removed, and the type of surgery (Table I). The histology of various parts of the samples was examined and all those in which tendon or perimysium predominated over muscle fibres were excluded. Lipids in the sections were visualized by oil-red-O or Sudan-black staining. LDH activity was measured by the reduction of the coenzyme NAD to NADH bound to LDH activity coupled with the transformation of leucotetrazolium into violet formazan. The solutions of reagents were the same as those used to stain gel-electrophoretic columns (Schrauwen, 1966).

The LDH isoenzymes were separated by acrylamide-gel electrophoresis, by the method of Davis (1964), on gel columns in pH 8·6 M tris buffer at 400 V and 5 mA. Duplicate analyses were performed, and the isoenzymes were stained according to Schrauwen (1966) under optimal conditions determined by pilot experiments. The proportions of the isoenzymes were determined by scanning with a Chromoscan (Joyce-Loebl) densitometer. The proportions of the H and M type subunits were calculated from the percentage of the five isoenzymes, taking into account the subunit content of each isoenzyme, according to the following:

sum of H subunits, $H = LDH_1 + \frac{3}{4}\,LDH_2 + \frac{1}{2}\,LDH_3 + \frac{1}{4}\,LDH_4$;

sum of M subunits, $M = LDH_5 + \frac{3}{4}\,LDH_4 + \frac{1}{2}\,LDH_3 + \frac{1}{4}\,LDH_2$.

For comparing the isoenzyme values and subunit

Table I *Extraocular muscle samples investigated, grouped according to diagnosis, refraction, and origin*

Diagnosis	*Age (years)*	*No. of samples*	*Refraction*	*Origin of sample*	*Surgery*
Esotropia, alternating	4–6	8	Emmetropia	Medial rectus	Recession
	4–14	6	Emmetropia	Lateral rectus	Advancement
Esotropia	6–14	11*	Hypermetropia	Medial rectus	Recession
	5–13	6*	Hypermetropia	Lateral rectus	Advancement
Exotropia, alternating	6–12	7	Myopia (<–6·0D)	Medial rectus	Advancement
Exotropia, monocular amblyopia	6–26	8	Myopia (between –6·0 and –12·0D)	Lateral rectus	Recession

*Five with uniocular amblyopia

Address for reprints: Dr I. L. Kahán, Department of Ophthalmology, University Medical School, Szeged, Hungary

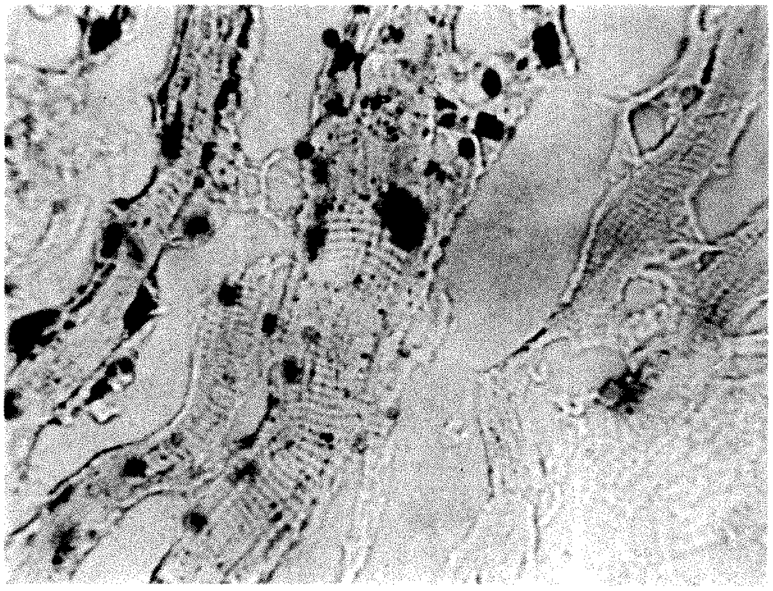

FIG. 1 *Cryostat section of human extraocular eye muscle sample. Orbital layer of muscle to left. Sudan black* ×600

ratios in the muscles from eyes with different refractions the one sample *t* test was used.

Results

In sections of extraocular muscles from emmetropic eyes the orbital layer (away from the globe) stained heavily with oil-red-O or Sudan-black while that adjacent to the globe stained scarcely at all (Fig. 1).

In both the medial and lateral rectus muscles of emmetropic and hypermetropic eyes the LDH_5- and LDH_4-type isoenzymes predominated, whereas in both the medial and lateral rectus muscles of myopic eyes the LDH_1 and LDH_2 isoenzymes were predominant (Fig. 2). Sample distributions of LDH isoenzymes and their proportions of subunits in medial rectus samples are shown in Table II. The proportion of M subunits in the LDH content of horizontal muscles of emmetropic and hypermetropic eyes was higher than that of H subunits, while in myopic eyes the proportion of H subunits was higher (Figs 3 and 4).

There was no significant difference between the LDH isoenzyme content of the medial and lateral rectus muscles of emmetropic eyes, or between that of corresponding muscles of emmetropic and hypermetropic eyes. On the other hand, the difference between the LDH isoenzymes, and therefore between the proportion of subunits, of emmetropic and myopic eyes was significant (Table III).

Discussion

The two different layers of the extraocular eye muscles that our study demonstrated agree with the findings of Scott and Collins (1973) of two functionally distinct compartments, the inner fibres securing the rapid (twitch) movements and the outer (orbital) the tonic contractions. We suggest that the former, adjacent to the globe and without appreciable lipid content, represent the white

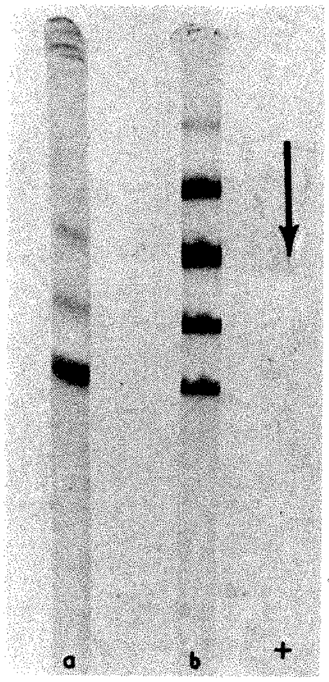

FIG. 2 *LDH isoenzyme patterns of* (a) *medial rectus of myopic eye, and* (b) *medial rectus muscle of hypermetropic eye*

Table II *Distribution of LDH isoenzymes and their subunit pattern in medial rectus muscle samples*

Refraction	*LDH isoenzymes (per cent)*					*Subunit (per cent)*	
	LDH$_1$	*LDH*$_2$	*LDH*$_3$	*LDH*$_4$	*LDH*$_5$	*M*	*H*
Emmetropia	6·8	12·0	19·0	21·0	41·1	69·3	30·7
	7·3	13·0	18·0	21·7	40·0	68·5	31·5
Hypermetropia	—	—	46·8	27·2	26·0	69·7	30·3
	—	—	48·8	20·2	31·0	70·5	29·5
Myopia	38·5	28·5	21·0	12·0	—	26·5	73·5
	37·0	28·6	21·0	13·4	—	27·6	72·4

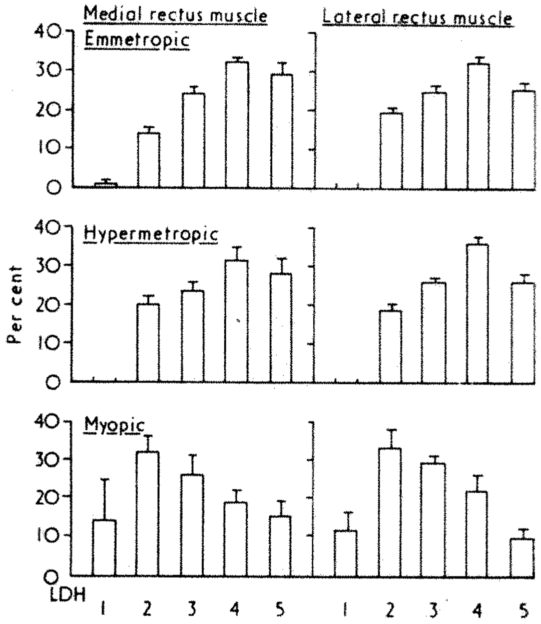

FIG. 3 *LDH isoenzyme distribution (per cent) in medial and lateral rectus muscle samples of emmetropic, hypermetropic, and myopic eyes. See Table I for number of samples*

muscle component and the latter, the lipid-rich orbital fibres, the red muscle component of the extraocular muscle.

This view is supported by the difference in the LDH isoenzyme pattern of the emmetropic-hypermetropic and the myopic extraocular eye muscles. The predominance of H subunits is consistent with an absent or decreased demand for rapid movements. White muscles are known to atrophy with inactivity, whereas red muscles do not. The effects of inactivity may be supposed to occur in the extraocular eye muscles in myopia. The excursions of the eye are reduced and myopes, unless their myopia is fully corrected, do not see remote objects; convergence-impulse consequent on accommodation is rare. All these factors may result in partial atrophy of the white muscle fibres (Briskey, Cassens, and Marsh, 1970). Moreover, progressive inadequacy of the capillary network, characteristic of the myopic choroid and retina, may also affect extraocular structures, including the eye muscles. The red muscle layer, with its richer capillary network, may survive, but the less vascular white muscle layer may succumb, leading to a predominance of undamaged red muscle fibres and H subunits.

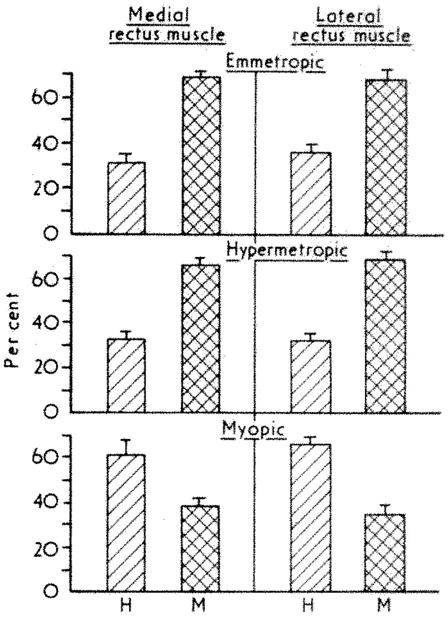

FIG. 4 *LDH, H and M subunits (per cent) in medial and lateral rectus muscle samples from emmetropic, hypermetropic, and myopic eyes. See Table I for number of samples*

Table III *Statistical differences between LDH and subunit values in medial rectus samples of emmetropic eyes and other muscle samples of eyes with various refractions (one sample* t *test;* $P < 0{\cdot}05$ *=significant,* $P > 0{\cdot}05$ *=not significant)*

Sample and refraction (no. of samples)	*Medial rectus, emmetropic eye (8 samples)*						
	LDH_1	LDH_2	LDH_3	LDH_4	LDH_5	H	M
Lateral rectus, emmetropia (6)	NS	NS	NS	NS	NS	NS	NS
Medial rectus, hypermetropia (11)	NS	NS	NS	NS	NS	NS	NS
Lateral rectus, hypermetropia (6)	NS	NS	NS	NS	NS	NS	NS
Lateral rectus, hypermetropia, amblyopia (5)	NS	NS	NS	NS	NS	NS	NS
Medial rectus, hypermetropia, amblyopia (5)	NS	NS	NS	NS	NS	NS	NS
Medial rectus, myopia (7)	NS	S	NS	S	S	S	S
Lateral rectus, myopia (8)	NS	S	NS	NS	S	S	S

S = Significant NS = Not significant

Summary

The lactate dehydrogenase isoenzyme patterns in 46 extraocular eye muscle samples removed at surgery for squint were determined by acrylamide-gel electrophoresis and reduction of NAD coupled with formazan reaction. Muscle type subunits predominated in the isoenzymes of the medial and lateral rectus muscles of emmetropic and hypermetropic eyes, whereas heart type subunits predominated in those of myopic eyes.

We thank K. Boda for mathematical analyses and E. Jójárt for technical assistance.

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Uveal colobomata and Klinefelter syndrome

M. S. HASHMI AND A. G. KARSERAS
From the University Department of Ophthalmology Welsh National School of Medicine

Most multiple congenital abnormality syndromes associated with uveal colobomata have their origins dating from before intrauterine development. Causative genetic and chromosomal influences were reviewed (James, Karseras, and Wybar, 1974), but associated abnormalities of the sex chromosomes were not observed in their series and are a rare occurrence in the literature. It is of interest therefore to record uveal colobomata occurring in a patient with Klinefelter syndrome and to discuss the possible implications. This association has not been recorded in Britain previously.

Material and methods

CASE REPORT

A 17-year-old White youth presented with concern about the lack of development of his external genitalia. Bilateral iris colobomata had been noted at birth and he had attended an ophthalmologist from that time. He had been wearing contact lenses for three years.

The parents were unrelated and there was no family history of ocular abnormality. Examination of both parents revealed normal eyes. The father and mother were both 45 years old at the time of his conception.

There was one normal brother, three years older, and the mother had had a diagnostic *x*-ray of the pelvis during the pregnancy of this child.

CLINICAL FINDINGS

The patient was of normal intelligence, pleasant personality, and heavily built (Figs 1 and 2). He weighed 79·3 kg and was 5 ft 8¾ in (175 cm) in height. He did not shave and had a high-pitched 'unbroken' voice. Axillary hair was scanty and pubic hair had a female distribution (Fig. 3). There was a mild gynaecomastia (Fig. 2). The penis was 6 cm in length, the testes 2·5 cm (Figs 3 and 4). Hormonal investigation revealed a pattern characteristic of late Klinefelter syndrome:

Plasma testosterone 167 mg/100 ml (normal 300 to 1200 mg/100 ml)
Plasma follicle stimulating hormone 19 units/litre (normal 5 to 10 units/litre)
Plasma luteinizing hormone 22·5 units/litre (normal 5 to 10 units/litre).

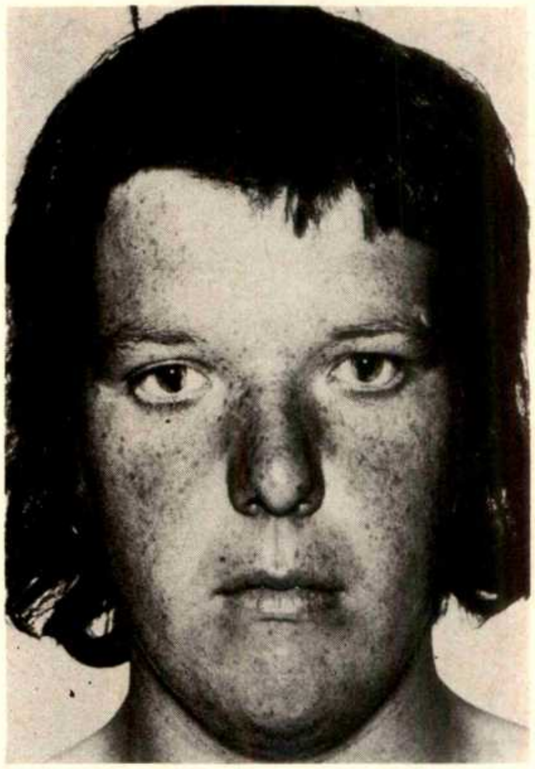


FIG. 1 *The patient*

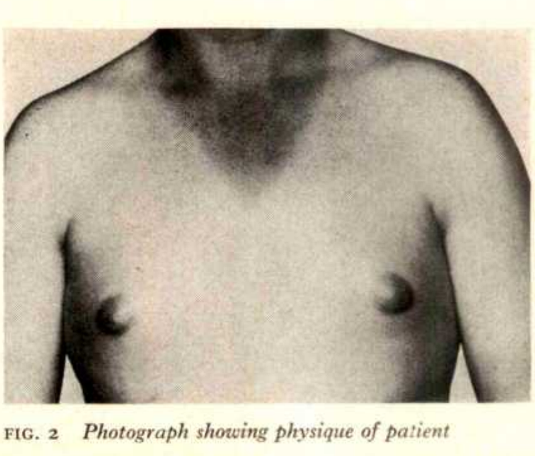
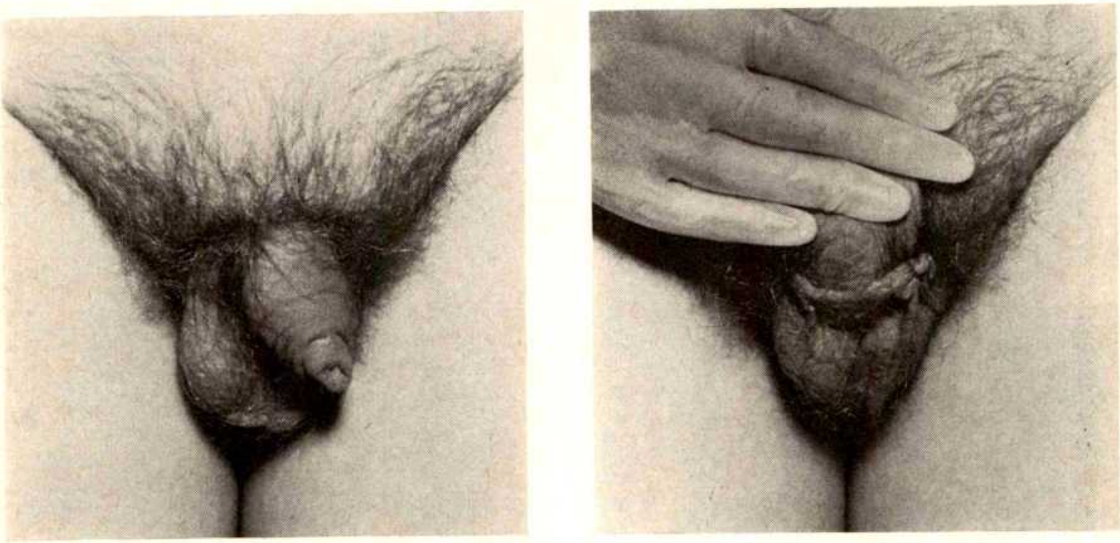


FIG. 2 *Photograph showing physique of patient*

Address for reprints: A. G. Karseras, University Department of Ophthalmology Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN



FIGS 3 and 4 *Photographs showing underdeveloped genitalia*

OPHTHALMIC FINDINGS

A right/alternating divergent squint was present. There were bilateral colobomata involving the iris and choroid (Figs 1 and 5). Although the choroidal colobomata did not quite extend to the optic discs, both discs were abnormal. The right disc and approximating colobomata are shown in Figs 6 and 7. Corrected visual acuity with -2·5D contact lenses was 6/36 right eye and 6/9 left.

CYTOGENETIC FINDINGS

The chromosomes of lymphocytes of a 72-hour peripheral blood culture were examined. One hundred satisfactory metaphase spreads were counted. In 98 cells there were 47 chromosomes (Fig 8). The extra chromosome belonged to the C group, and was identified as an X-chromosome by the trypsin Giemsa banding technique.

Two counts revealed 46 chromosomes, one was minus a G-group chromosome (? 46 XX) one was minus a C-group chromosome (? 46 XY). These were felt to be due to random loss rather than mosaicism.

Discussion

The association of Klinefelter syndrome and uveal colobomata has been recorded previously (François, Matten-Van Leuven, and Gombault, 1970). It is a rare association but these authors recorded the fourth case in the literature, and after reviewing the incidence of uveal colobomata and Klinefelter syndrome as separate entities, they concluded that the probability of a chance association was in the region of one in six million. They felt that the coloboma might occasionally be part of the phenotypic expression of Klinefelter syndrome. The association of two preuterine induced conditions (see below) enhances the view that this is not a chance association.

The theoretical possibilities which might explain the association of uveal colobomata with Klinefelter syndrome are:

1. The mother may have been a carrier of the X-linked gene for uveal colobomata, and the patient may have been homozygous for this gene ($X^{M1}X^{M1}Y$). However, there was no family history of colobomata in the mother's family and the other manifestations of this X-linked gene (Goldberg and McKusick, 1971) such as mental

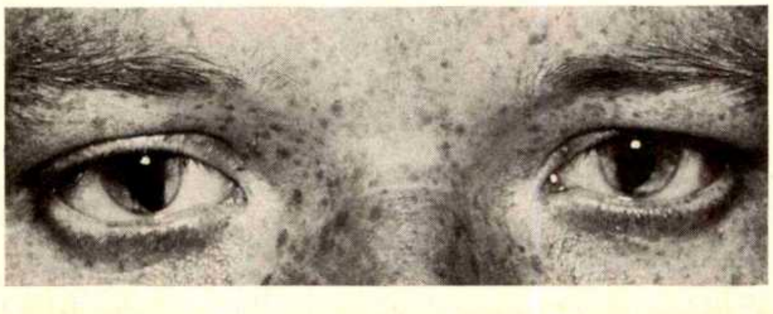
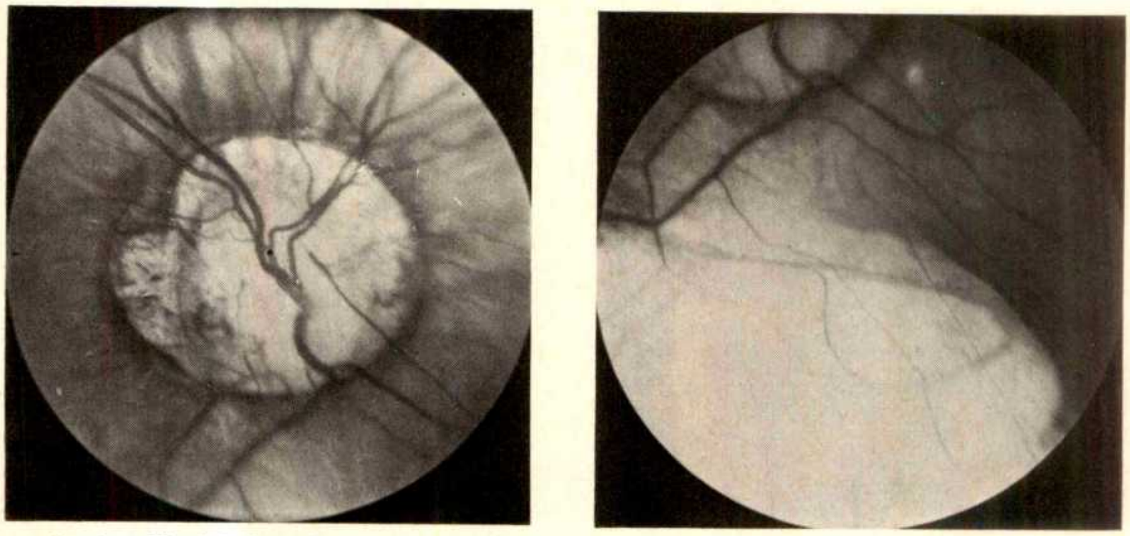


FIG. 5 *Photograph showing bilateral colobomata involving the irides*



FIGS 6 and 7 *The right disc and approximating colobomata*

retardation were absent. Furthermore, only 10 per cent of Klinefelter patients have identical X chromosomes from the mother (Hamerton, 1971).

2. The extra X chromosome may occasionally influence the genetic mechanisms involved in the closure of the optic cleft. This theory is supported by the known quantitative effect of heterochromatin on cell growth and development (Mittwoch, 1967) and the association of other closure defects with diverse chromosomal aberrations.

3. The environmental influence which occasioned gametogenetic non-dysjunction may also have had a mutogenic effect on the genetic mechanisms involved in the closure of the optic cup.

Either of the last two possibilities would explain the occasional but not fortuitous association of uveal colobomata with Klinefelter syndrome.

The chromosomes of the patient have been shown to be XXY. Forty per cent of such patients have the extra chromosome derived from non-dysjunction of the male parent during spermatogenesis. In 50 per cent of patients both (non-identical) X chromosomes are derived from the mother indicating that non-dysjunction must have occurred during the primary division of oogenesis (Hamerton, 1971). In the 10 per cent of Klinefelter patients with identical X chromosomes from the mother, non-dysjunction could have occurred during the second

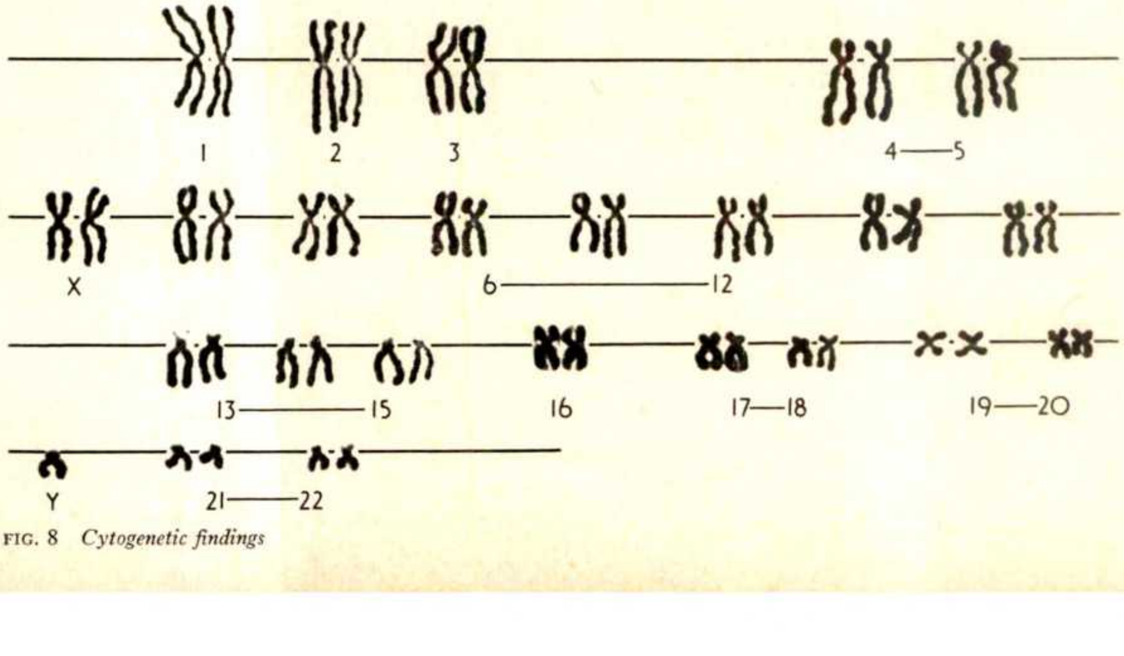


FIG. 8 *Cytogenetic findings*

meiotic division of oogenesis or early after zygote formation. In the latter instance mosaicism would be produced and the non-viable X O cell line would leave an XXY constitution. (François and others (1970) had to consider the possibility of a post-zygotic origin in their case as an apparent mosaicism was present. If the mosaicism was not a cultural artefact, their acknowledged possibility of the mosaicism arising from an imbalanced gamete would seem most likely.)

Thus over 90 per cent of Klinefelter syndromes have an established preuterine origin. These studies have been undertaken by investigating the distribution of the dominant X-linked blood group (Xg) in the parents and the child. Unfortunately, both parents of our patient were Xg negative and the parental source of the extra X chromosome could not be ascertained. However, it remains extremely likely that the patient exhibits yet another example of the association of a preuterine induced, congenital syndrome with the uveal colobomata.

It is of interest to discuss the environmental influences which have been alleged to cause uveal colobomata during early pregnancy. Cullen (1964) described uveal colobomata usually with major limb dysgenesis, occurring as a result of thalidomide. In the absence of a definite thalidomide history (Cullen, 1964—Case 2) major limb defects have been taken as presumptive evidence of a thalidomide origin. However, such defects occurred before the advent of thalidomide (Gilkes and Strode, 1963; Case 7—Table I), and limb abnormalities have often been described in systemic syndromes associated with uveal colobomata (James and others, 1974). Many of the series of patients with limb defects and uveal colobomata reviewed by Cullen (1967) may not be attributable to thalidomide; and Case 2 (Table III) particularly fitted all the clinical criteria for the 'oculo-anal' syndrome and the absence of thalidomide was notable. The 'oculo-anal' syndrome has been shown to have an abnormal chromosomal complement (Schachenmann, Schmid, Fraccaro, Mannini, Tiepolo, Perona, and Sartori, 1965).

It may be, as Cullen (1967) suggested, that thalidomide acts primarily not as a teratogenic agent, but in an immunosuppressive capacity and allows normally aborted pregnancies to proceed to term. Such abortions often have chromosomal abnormalities (Howard, Boué, Deluchat, Albert, and Lahov, 1974). It would be interesting, therefore, if chromosomal studies could be undertaken on thalidomide babies, particularly those with colobomatous defects.

The occasional reports of infections, such as herpes simplex during pregnancy, as a cause of uveal colobomata may be chance associations and remain to be substantiated (Fraser and Friedmann, 1967).

The likelihood is that very few uveal colobomata have their primary origin during embryogenesis, and that most arise from inherited genetic, sporadic (mutational) genetic, or chromosomal abnormalities during spermatogenesis and oogenesis. Inquiry into possible environmental agents must therefore include these periods of gametogenesis in the male and female as well as the period of intrauterine development of the fetus.

Treatable endocrine dysgenesis occurring in syndromes where uveal colobomata can occur has been emphasized previously (Karseras and Laurence, 1975). The present patient has suffered great emotional trauma from his defective gonadal development. Fortunately, much of the abnormality of his primary and sexual development is reversible with the administration of testosterone. Sterility, but not impotence, will persist. Earlier diagnosis would have removed much of the patient's concern.

We thank Dr Ruth Sanger for establishing the Xg blood groups in this study, Dr Peter Harper for his helpful criticism of genetic concepts, and Mr Selwyn Roberts for undertaking the cytogenetic analysis. We are grateful to Dr J. Picton Thomas for his permission to publish this case and for his helpful discussion of the endocrine features.

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Causes of blindness among students in blind school institutions in a developing country

MOSES C. CHIRAMBO AND DAVID BENEZRA*
From the Department of Ophthalmology, Queen Elizabeth Central Hospital, Blantyre, Malawi

Genetic factors are the main causes of childhood blindness in developed countries (Sorsby, 1966; Fraser and Friedmann, 1967; Merin, Lapithis, Horowitz, and Michaelson, 1972; Goldstein, 1972). In developing countries infections as causes of blindness in childhood outnumber the genetic factors (Rodger, 1959; Phillips, 1961; Wilson, 1962; Olurin, 1970). Malnutrition in these countries resulting in xerophthalmia and keratomalacia is also an important cause of blindness (Awdry, Cobb, and Adams, 1967; *WHO Chronicle*, 1973).

Since the early 1960s the Eye Department of the Hadassah Hebrew University Hospital in Jerusalem has been sponsoring the ophthalmological care in many African countries (Michaelson, 1972). In Malawi sponsoring started in 1965. After 10 years a study was undertaken in order to evaluate the causes of blindness in the past, the current causes of blindness, and to assess the expectations for the future.

We report here a retrospective study on the causes of blindness as presented by students in blind school institutions all over Malawi.

Patients and methods

Two hundred and seventy students attending 17 blind school institutions were examined. The location of these schools is shown in the Figure. Admission to them is non-selective and depends on the number of vacant places available at the time of application. However, the following conditions play a role as selective factors. (1) Owing to tradition and culture fewer females than males apply. Therefore the relative proportion between sexes in this study does not reflect the real situation. (2) Blindness due to causes that may influence the life expectancy will not be found and their contribution to 'all' causes of blindness will not be shown in this study. (3) Admission to the blind schools is generally at the age of 4 to 6 years, therefore most cases will represent mainly the causes of blindness in childhood.

The criteria for admission to the blind school institutions are good health and sight of 1/60 or less in the better eye. Until this study this selection was arbitrarily performed by the teachers of the schools or the medical assistant. The students were not examined by an ophthalmologist before admission. We think that the students in these institutions represent an adequate picture of the main causes of childhood blindness in Malawi in the past.

We examined all students attending the above schools during the period from June to December 1975. The examination included a testing of visual acuity, external examination, tonometry, and ophthalmoscopy. These

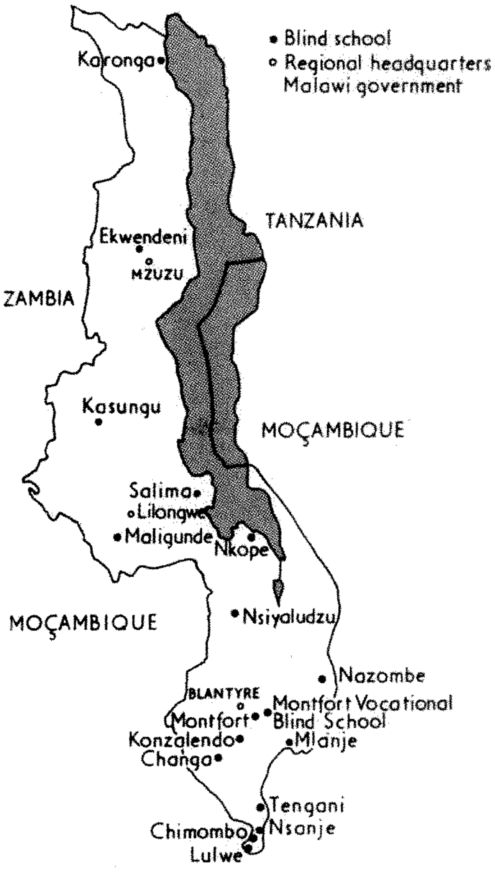

FIGURE *Location of blind school institutions in Republic of Malawi*

This work was supported by the Ministry of Health, Malawi, and the Jerusalem Institute for the Prevention of Blindness, Jerusalem, Israel

Address for reprints: D. BenEzra, MD, PhD, Department of Ophthalmology, Hadassah HU Hospital, Jerusalem, Israel

*Dr BenEzra is on leave from the Department of Ophthalmology, Hadassah Hebrew University Hospital, Jerusalem, Israel were performed in the school. When necessary, doubtful cases needing further investigation were referred to the eye department of the Queen Elizabeth Central Hospital in Blantyre. Histories were obtained from the patients, school records, and, when possible, from relatives or parents.

Results

Seventy-three per cent of the students lost their vision before the age of three. Only 15·9 per cent were blind after the age of six (Table I). Ocular infections were responsible for 75·2 per cent of all cases of blindness. Measles was the underlying factor in 43·7 per cent, while smallpox was found in 5·2 per cent (Table II). A history of ocular infection (most probably bacterial), including ophthalmia neonatorum, was obtained in 26·3 per cent. In most of these cases a history of use of traditional medicine was obtained. Practically none of these cases was examined in the acute stage by an ophthalmologist or an ophthalmic assistant. The extensive scarring along with the symblepharon seen in many cases was most probably due to the aggravating effect of the instillation of the traditional medicine. Hereditary causes were found in 21 cases (7·8 per cent). Congenital cataracts were responsible for 2·6 per cent while optic atrophy of unknown cause was found in eight cases (3·0 per cent). The prevalence of microphthalmos and macular degeneration was 1·5 and 0·7 per cent, respectively (Table II). Forty-six cases (17·0 per cent) were classified as 'unspecified' as the cause of the blindness was unknown. In some of these a history was impossible to obtain.

Table I *Age at onset of blindness among 270 students*

Age (years)	*Male*		*Female*		*Total*	
	No. of cases	*Per cent*	*No. of cases*	*Per cent*	*No. of cases*	*Per cent*
< 1	25	9·3	8	3·0	33	12·3
1–3	110	40·7	54	20·0	164	60·7
4–6	23	8·5	7	2·6	30	11·1
> 6	36	13·3	7	2·6	43	15·9
Total	194	71·8	76	28·2	270	100

Table III *Aetiology and suggested intervention in 37 blind students having some hope of partial recovery of vision*

Diagnosis	*Aetiology*	*No. of cases*	*Suggested intervention*
Total leucoma cornea	Measles	9*	Corneal grafts
	Bacterial infection	6	Corneal grafts
	Smallpox	1	Corneal grafts
Leucoma centralis adherens	Measles	5	Optical iridectomy
	Bacterial infection	4	Optical iridectomy
	Smallpox	2	Optical iridectomy
Congenital cataract	Hereditary	5	Aspiration of lenses
	Hereditary	2†	Refraction
Complicated cataract	Unspecified	1	Aspiration of lenses
Corneal dystrophy	Hereditary	1	Corneal graft
High myopia (albino)	Hereditary	1	Refraction

*Any patient having some hopes for recovery of vision, at least in one eye, was considered as one case

†In these two cases lenses were aspirated previously. However, as they were not provided with glasses they were considered as blind (see also Table IV)

Table II *Causes of blindness according to age and sex in 270 students*

Causes	*Age (years)* 10		11–15		16–20		20		*Total*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*No.*	*Per cent*
Measles*	23	19	32	17	16	7	2	—	118	43·7
Smallpox*	—	—	6	3	2	1	2	—	14	5·2
Bacterial infections*	4	3	20	6	16	2	20	—	71	26·3
Congenital cataract	2	1	1	1	1	—	1	—	7	2·6
Microphthalmos	—	2	—	1	1	—	—	—	4	1·5
Optic atrophy	—	1	3	—	1	—	3	—	8	3·0
Macular degeneration	—	—	—	—	—	—	2	—	2	0·7
Unspecified	11	6	9	5	7	—	8	—	46	17·0
Total	42	32	71	33	44	10	39	—	270	100·0

Measles was implicated as a cause of blindness in each case where a history of blindness after measles infection was obtained

Smallpox was implicated as a cause of blindness in each case where a history of blindness after smallpox infection was obtained

Bacterial infections were implicated as a cause of blindness when a history of ocular 'infection' without any systemic involvement was obtained

*Most of these cases used local medicine as the first attempt for treatment. Some of them sought treatment in hospital at a later stage

Table IV *Resulting visual acuity after intervention in 11 cases*

Diagnosis	*Aetiology*	*Visual acuity before intervention*		*Intervention*	*Visual acuity after intervention*		*Comments*
		Right	*Left*		*Right*	*Left*	
Leucoma adherens right eye	Measles	PL	—*	Optical iridectomy	1/240	—	Vitreous organization
Leucoma adherens both eyes	Measles	1/60	PL	Optical iridectomy	6/24	HM	Vitreous opacities left eye
Leucoma adherens both eyes	Measles	1/60	2/60	Optical iridectomy	6/60	6/36	
Leucoma adherens right eye	Measles	1/120	—*	Optical iridectomy	4/60	—	
Leucoma adherens both eyes	Smallpox	PL	2/60	Optical iridectomy	HM	6/18	Cataract right eye
Leucoma adherens both eyes	Bacterial infection	PL	PL	Optical iridectomy	6/60	HM	
Complicated cataract	Unspecified	PL	PL	Aspiration	PL	PL	Retrolental organization both eyes
Congential cataract	Hereditary	2/60	1/60	Refraction	5/60	6/60	State after aspiration both eyes†
Congenital cataracts	Heriditary	1/60	1/60	Refraction	4/60	4/60	State after aspiration both eyes†
Congenital cataracts	Hereditary	PL	PL	Aspiration	4/60	4/60	
Congenital cataracts	Hereditary	PL	PL	Aspiration	4/60	4/60	

*Phthisis bulbi PL = perception of light HM = hand movements

†In these two cases lenses were aspirated previously. However, as they were not provided with glasses they were considered as blind (see also Table III)

Among the 270 students examined we found that 37 cases (13·7 per cent) should have a trial of surgical intervention (Table III). Eleven patients were surgically treated; nine of them regained useful vision (Table IV). We estimated that a further 26 cases could be similarly helped.

Discussion

Measles as a cause of blindness was found in 43·7 per cent of the cases in our study. Earlier surveys in Zambia incriminated this virus as a cause of blindness in 81·3 per cent (Phillips, 1961). Traditional medicine is still widely used in Malawi, although to a progressively less extent. 'Fresh' cases presenting after the instillation of some traditional medicines often give a picture of acid or alkaline burn. During a period of a few months we saw 30 cases where both corneae were destroyed and uvea prolapsed as a result of the use of traditional medicine for the treatment of bilateral ocular infection. The best outcome in these cases is a total vascularized leucoma or a large anterior staphyloma, and the worst (unfortunately the most common) phthisis bulbi (Chirambo and BenEzra, to be published).

Despite the widespread use of traditional medicine and its still important role in the induction of childhood blindness in Malawi, the high frequency of blindness due to infectious agents (plus traditional medicine) as found in this study and in that of Merin (1967) has dropped drastically during the last 10 years. From an incidence of at least 300 blind children per 100 000 in the early 1960s the incidence has dropped to 34 cases per 100 000 children under five years of age (BenEzra and Chirambo, to be published).

We evaluated 13·7 per cent of the blind students as having some chances of partial recovery of vision. A preliminary attempt has shown that in nine cases out of 11 treated a useful vision of 4/60 to 6/18 in the better eye has been restored. This vision will enable most of these patients to conduct a normal life. Clearly, any future applicant to the blind school institutions should be examined by an ophthalmologist before admission.

Summary

Out of 270 students in 17 blind school institutions in Malawi 73 per cent were blind before the age of three. The most common cause for the blindness was ocular infection (75·2 per cent). Measles, as a single cause, was responsible for 43·7 per cent of the cases and smallpox for 5·2 per cent. Bacterial infections were incriminated in 26·3 per cent of the

cases. Most of these had received traditional medicine during the acute phase of the disease. Hereditary factors as causes of blindness were found in 7·8 per cent of the cases. These included congenital cataracts (2·6 per cent), optic atrophy of unknown origin (3·0 per cent), microphthalmos (1·5 per cent), and macular degeneration (0·7 per cent).

Careful ophthalmological examination showed that in 37 cases an intervention could be attempted in order to improve the vision. In the 11 most favourable cases this was attempted, with the result that nine cases gained a useful vision of 4/60 to 6/18 in the better eye.

We thank Professor I. C. Michaelson, Head of the Jerusalem Institute for the Prevention of Blindness, for his support and advice.

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Book reviews

Advances in Ophthalmology, vol. 32. Edited by E. B. STRIEFF. 1976. Pp. 203, 52 figs, 28 tables, refs. Karger, Basel ($49·25)

Like several of its predecessors in this series, this book comprises a collection of articles on a variety of subjects. Three papers deal with contact lenses: Aquavella reviews the present role of hydrophilic lenses and provides a comprehensive list of references; there is a short paper by Enoch on the use of soft lenses, together with a list of inverted telescope units used in the correction of uniocular aphakia. The third is a longer paper by Gernet on the value of combined contact lens correction for unilateral aphakia which has advantages over the more conventional type of aphakic correction, and the optical principles underlying this type of lens prescription are dealt with in depth.

There is an interesting article by Tenner demonstrating the value of fluorescein angiography in the study of the glaucomatous optic disc, although the author concedes that the technique is not suited to routine diagnosis.

In the remaining two papers there is a discussion on pneumatonography by Langham, Leydhecker, and their associates as part of a collaborative study between centres in Baltimore and Wurzburg. The studies investigated postural changes in intraocular pressures which show significant differences in normal and glaucomatous eyes.

The last article by Zingirian discusses ocular pemphigus with several case presentations describing the disease and its treatment.

The criticism that has been levelled against this series still applies. Although there is no question of the high standard of the individual contributions, particularly in this volume, each subject is very specialized and therefore the book is likely to have only a limited appeal. Sadly also, the fact that three of the six articles are in German, restricts the amount of information that can be derived by the average English-speaking ophthalmologist.

T. J. FFYTCHE

Advances in Uveal Surgery, Vitreous Surgery, and the Treatment of Endophthalmitis. By G. A. PEYMAN, D. R. SANDERS, and M. F. GOLDBERG. 1975. Pp. 238, figs, tables, refs. Appleton Century-Croft, New York (No price given)

At a time when a number of instruments have become available for vitreous surgery and the development of this method of treatment is being actively pursued, it is of particular interest that a book should be published in which a large section is devoted to vitreous surgery, including a description of the use of an instrument developed by one of the authors.

The chapters on uveal and vitreous surgery start with a short consideration of the anatomy of the respective structures and with a discussion of the diseases. In considering uveal surgery attention is largely devoted to management of malignant melanomata of the iris, ciliary body, and choroid. Modern techniques of conservative treatment are fully discussed. In the chapter on vitrectomy the use of the vitrophage for lensectomy and in the treatment of vitreous disease is considered in sufficient detail to provide the reader with adequate practical information about the techniques.

The last section is devoted to the treatment of endophthalmitis. Several antibiotics are described and the more important ones are discussed with particular reference to their effectiveness when given by the intravitreal route. The duration of their activity and possible toxic effects are also discussed. This chapter is particularly valuable for the detailed manner in which each drug is considered. The technique of intravitreal injection, an important factor in avoiding adverse effects, is fully described.

Each section of the book includes a full and up-to-date list of references. The text is well illustrated and the pictures have excellent captions.

This is a book which is written by authors who have practical experience in the fields of which they write. It should make equally helpful reading for both the postgraduate student and the practising consultant.

JAMES R. HUDSON

The Changing Status of the Blind from Separation to Integration. By B. LOWENFELD. 1975. Pp. 336, figs, tables. Thomas, Springfield ($23·50)

This book traces the care of the blind from earliest times to the present day. Among primitive peoples, the blind, like other physically handicapped persons, were often killed. Many famous people in early times were blind, including Homer, but a large proportion of blind persons had to sustain themselves by begging. In early Christian times blindness was regarded as a punishment for some misdemeanour and was in fact inflicted as a punitive measure in some cases. The family looked after their blind persons. The Jewish people always tried to mitigate the bitter fate of the blind. During the Middle Ages hospitals for the blind were opened in Europe and some public responsibility for their care became manifest. In the seventeenth century some blind individuals acquired education and showed outstanding achievements in various fields of endeavour. Provision of work for the blind came to be recognized as necessary and there was some advance in the means of communication among the blind. The first school for blind children was founded in 1784 by Valentin Härg. Raised print was introduced and was useful in teaching, and this school prepared blind children for employment. The introduction of an embossed dot alphabet by Louis Braille was a great advance. Many new schools for the blind were opened in the early nineteenth century.

The next stage evolved as a recognition that blind people must be given equal opportunities to those of the sighted, and it is contended that this has now been achieved in the United States of America. In about 1830 three private schools for the blind were opened in the United States, and in general these followed the pattern of those already working in Europe. The first director of the Perkins Institution in Boston was Samuel Gridley Howe who did much to integrate the blind into the life of the general population. He was responsible a few years later for the opening of the first state school for the blind in Columbus, Ohio. Craft training was very important in these early blind schools, and has continued to be an essential part of blind training. Some blind people lived and worked in blind institutions and finished their lives in homes for the aged blind. As time passed the blind were encouraged to live and work independently and not only by handicrafts. The importance of a family life for the blind is now receiving great attention.

A. G. CROSS

Diagnostic Ultrasonics: Principles and Uses of Instruments. By W. N. McDICKEN. 1976. Pp. 320, figs, tables, refs. Granada Publishing, St Albans (£15)

Although Dr McDicken is a hospital physicist he is accustomed to teaching doctors and radiographers and his book is designed to meet the needs of a similar readership. Two radiologists taking up ultrasonic work vouch for the suitability of the book for beginners.

Only a small proportion of the book is relevant to ophthalmology and the eight entries in the index under eye refer to very superficial accounts, apart from a paragraph on transducers in eye work.

With the increasing acceptance of ultrasonic diagnosis a book of this type is very suitable for hospital libraries and ophthalmologists should support its purchase. For their own use, however, their money would be better spent on one of the books on ultrasonography in ophthalmology.

DOUGLAS GORDON

Essentials of Clinical Neuro-Ophthalmology. By A. H. WOLINTZ. 1976. Pp. 198, figs, tables, refs. Little Brown, Boston ($12·50)

The aim of this book is to introduce the commoner neuro-ophthalmological problems to ophthalmologists, neurologists, and neurosurgeons who are beginning their specialty training; as such it succeeds admirably. Any book of this type is bound to be incomplete in detail although the author overcomes this by the liberal use of lists, some of the contents of which may not be included in the text. The bias of several sections is unduly weighted by this incompleteness—for example, chiasmal lesion is the only cause for changes in refraction mentioned.

The layout of the book is good but the construction of each chapter and section is often not completely clear mainly because of the large amount of information that the author succeeds in including. The few diagrams are clear, and there is a carefully selected bibliography for those whose enthusiasm has been excited by this useful and concise book.

DAVID TAYLOR

Handbook of Perception, vol. V, Seeing. Edited by E. C. CARTERETTE and M. P. FRIEDMAN. 1975. Pp. 527, figs, tables, refs. Academic Press, London and New York ($28·50)

This book on visual perception is part of a multi-volume treatise concerning human perception. It is written mainly for psychologists and perhaps natural scientists in general. Contributions to ophthalmology appear to be negligible. Altogether 11 authors have contributed 12 chapters on subjects ranging from the history and contemporary theoretical problems of research into seeing to painting and photography, sandwiching the measurement of visual stimulus, the neural basis of seeing, temporal and spatial resolution, and the perception of pattern, colour, space, and motion.

The arrangement and the choice of the chapters throughout the book is somewhat arbitary and there is no synchronized theme running through the different chapters dealing with similar and related subjects. For example, the chapter by J. G. Robson dealing with the receptive fields of cells in the visual nervous system consists of a somewhat dogmatic review of the literature and the visual system is viewed as a spatial frequency analyser with modest capabilities. This is completely divorced from the chapter by J. P. Thomas dealing with the psychophysics of spatial resolution in human subjects with attempts to interpret this in terms of the receptive field organization of cells in the nervous system. Similarly, the chapter by R. L. and K. K. De Valois provides a comprehensive review of studies on the behaviour of colour-coded cells in the visual system and its relationship to the psychophysics of colour vision, but is completely divorced from the chapter by R. M. Boynton which deals with the physical, psychological, and physiological basis of colour, hues, and wavelengths.

The chapters dealing with temporal factors by L. Ganz, spatial factors by J. Thomas, three-dimensional depth and space factors in seeing by W. Richards, and also somewhat abstruse phenomena of pattern and object perception such as 'perceptual constancies' and 'illusions' by P. C. Dodwell take a basically bioengineering approach to these subjects.

The chapter on the measurement of the visual stimulus by Y. Le Grand includes much theoretical detail of the physics of light and radiometric concepts but fails to give more practical information about different types of visual stimuli and the methods of measurement required in research on seeing.

The chapter by P. C. Dodwell on contemporary theoretical problems comes to terms with the fact that there is still a wide gap between our understanding of perception and our ever increasing knowledge about the neurophysiology of the visual system. This view is shared by the authors of some of the other chapters. However, the present impetus to research on seeing appears to be coming from recent neurophysiological studies of the nervous system as is evident from the fact that practically all the chapters attempt to correlate perceptual phenomena with recent neurophysiological data. An excellent example is the chapter by R. Sekular on visual motion perception which emphasizes the recent neurophysiological evidence on the parallel processing of spatial details and temporal factors by two different classes of neurones in the afferent visual nervous system, and integrates this with well defined and controlled psychophysical experiments on pattern and motion.

The book begins with a chapter by Y. Le Grand on the history of research on seeing and ends with a chapter by M. H. Pirenne on vision and art. These two chapters are the most refreshing and readable chapters in the entire book. However, the reader who may have started with the hope of arriving at a clear picture of the results of many years of research on seeing will be left within a pool of detailed, conflicting, and poorly organized data.

A list of references at the end of each chapter may provide a useful source, though the choice of the references is always influenced by the personal views of each author.

H. IKEDA

Principles and Practice of Optical Dispensing and Fitting, 3rd ed. By L. S. Sasieni. 1975. Pp. 589, figs, tables. Butterworth, London (£15)

This book covers a wide scope and there is a comprehensive survey of materials and types of frames, but out-of-date photographs have been used.

The chapters on rules and facial measurements are enlightening for learners for whom this book is primarily written, and the revision sections at the end of chapters are useful. The survey of lenses available is comprehensive and a chapter on vision screeners is welcome.

The price, however, puts this edition in the category of a book to which a student would refer, but not necessarily be able to purchase.

J. A. MORRIS

Rational Diagnosis and Treatment. By H. R. Wulff. 1976. Pp. 182, 25 figs, 18 tables, refs. Blackwell, Oxford (£3·75)

As the author states in his introduction, the aim of this book is to emphasize that clinical decision-making must be as rational as possible, and to that end the doctor should have a clear idea of the reliability of the data obtained from the medical history, physical examination, and laboratory tests as well as the process by which a diagnosis was made so that suitable treatment can be selected. Although the examples are largely drawn from gastroenterology, the critical approach to the decision-making process is applicable in any clinical field.

Of necessity, statistical evaluation is given prominence, but the clear explanation of the methods used should not deter the non-mathematical reader. The chapters on diagnosis and the assessment of new diagnostic methods are particularly interesting, and if the critical approach outlined in this book were more widely adopted, patients would be spared many uncomfortable and expensive investigations. The evaluation of treatment, particularly the interpretation of reports of clinical trials is well discussed, and the importance of controlled therapeutic trials emphasized. All clinicians will find this book stimulating and interesting.

E. S. PERKINS

The Squinting Child. By R. Bruckner. 1976. Pp. 78, 20 figs. Schwabe, Basel and Stuttgart (18 fr)

This small book is designed to inform parents, nurses, social workers, and teachers about the problem of squints. The anatomy and physiology of the visual apparatus is described in simple terms with the aid of a few diagrams. The pathogenesis of squint and the non-surgical and surgical methods of treatment are discussed. This is an unpretentious book, demanding little knowledge and providing useful information for those concerned in school clinics and in social work among children.

T. J. FFYTCHE

Techniques of Anophthalmic Cosmesis. Edited by P. Guibor and M. Guibor. 1976. Pp. 232, figs, refs. Stratton, New York (No price given)

This is one of the first textbooks to be almost totally confined to the techniques of an ophthalmic prosthesis. Of especial interest will be those techniques described in congenital anophthalmia and the modifications to the moulded prosthesis to correct ptosis sulcus retraction after enucleation. Some surgical techniques are described but, in most instances, these are brief and help to embellish the text; I hope that at some future date a text entirely devoted to the prosthetics will become available. It would appear that the technique of enucleation, evisceration of the eye and orbit has been neglected; as an end procedure this has special relevance to the younger person and his future life in society and is therefore important.

MONTAGUE RUBEN

Vision and Acquisition: Fundamentals of Human Visual Performance, Environmental Influences, and Applications in Instrumental Optics. By I. Overington. 1976. Pp. 380, figs, tables, refs. Pentech Press, London (£14)

This book gives a detailed mathematical and physical account of the factors which modify vision. As only some 6 per cent of the account relates to the basic properties of the human visual system, it has but limited interest for ophthalmologists.

However, it is of great value, firstly to those engaged in the design of optical instruments, and secondly, to those interested in the factors which affect visual perception under difficult viewing conditions, such as object movement and atmospheric turbulence.

R. FISHER

Brit. J. Ophthal. (1976) **60,** 672

Correspondence

Aqueous humour lactic dehydrogenase isoenzymes in retinoblastoma

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, Since submitting our paper for publication, we have become aware of additional relevant information we wish to bring to your attention.

We have had the opportunity to study two patients whose aqueous humour assays are at variance with our previously-reported findings. One patient, with histologically proved retinoblastoma had a total aqueous humour LDH of 2303 iu/l and a ratio LDH_5: LDH_1 of only 1·9. The other patient, with bilateral congenital/non-rhegmatogenous retinal detachment and no retinoblastoma, had total aqueous humour LDH levels of 194 and 19, and ratios LDH_5: LDH_1 of 24 and 30.

A recent paper (Swartz, Herbst, and Goldberg, 1974) supported the original hypothesis of Dias, Senthe Shanmuganathan, and Rajaratnam (1971) that retinoblastoma is associated with an elevated total aqueous humour LDH, and referred to a paper by Kaneko and Suzuki (1972) who found (as we did) that, although the total aqueous humour LDH was inconsistently raised in retinoblastoma, in seven cases all were associated with an elevated LDH_3 isoenzyme (and to a lesser extent LDH_2 and LDH_4 fractions).

We believe that the aqueous humour LDH assay is currently a valuable diagnostic adjunct in the diagnosis of retinoblastoma, in that both an absolute elevation of the total aqueous humour LDH and a relative elevation of the slow isoenzyme fractions—that is, a shift to the right—appear to be suggestive *but not diagnostic* of retinoblastoma. We wish to encourage further experience with this test to resolve the inconsistencies in the literature, and to define more accurately the limits of reliability and scope of application of this biochemical assay.

Yours faithfully,

PAUL E. ROMANO and JACK KABAK
The Children's Memorial Hospital,
2300 Children's Plaza,
Chicago,
Illinois 60614, USA

(Undated, received 13 *September* 1976*)*

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DIAS, P. L. R., SENTHE SHANMUGANATHAN, S. S., and RAJARATNAM, M. (1971) *Brit. J. Ophthal.*, **55,** 130

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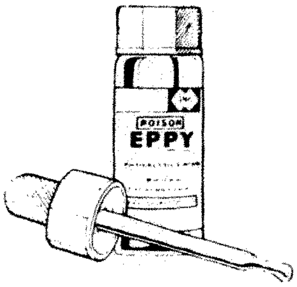

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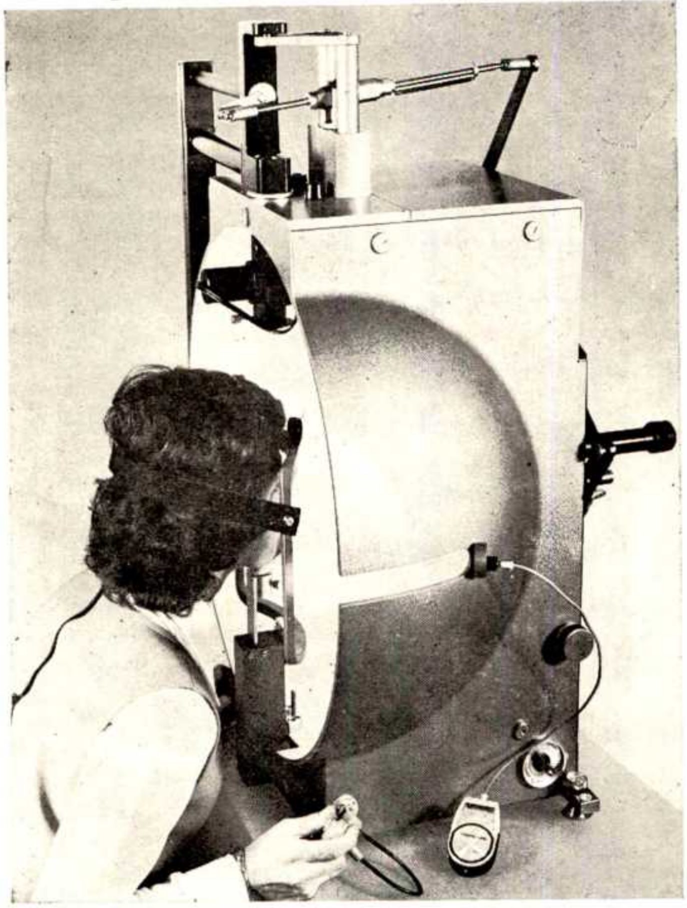

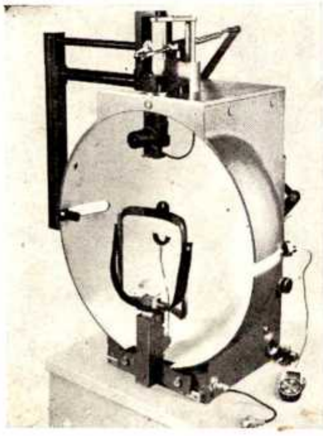

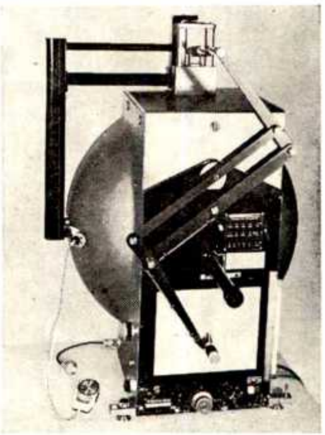

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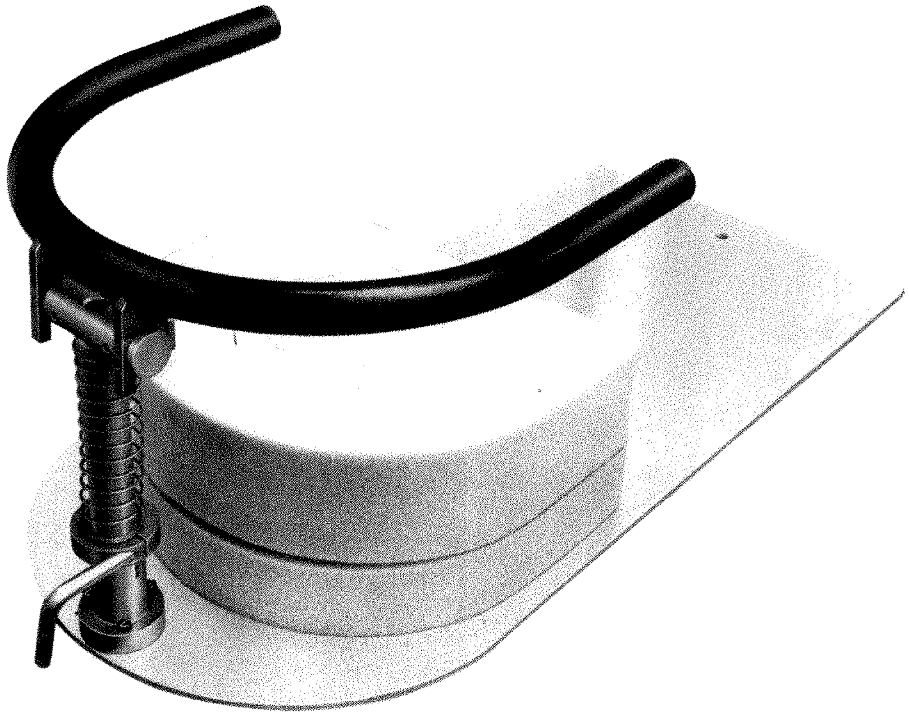

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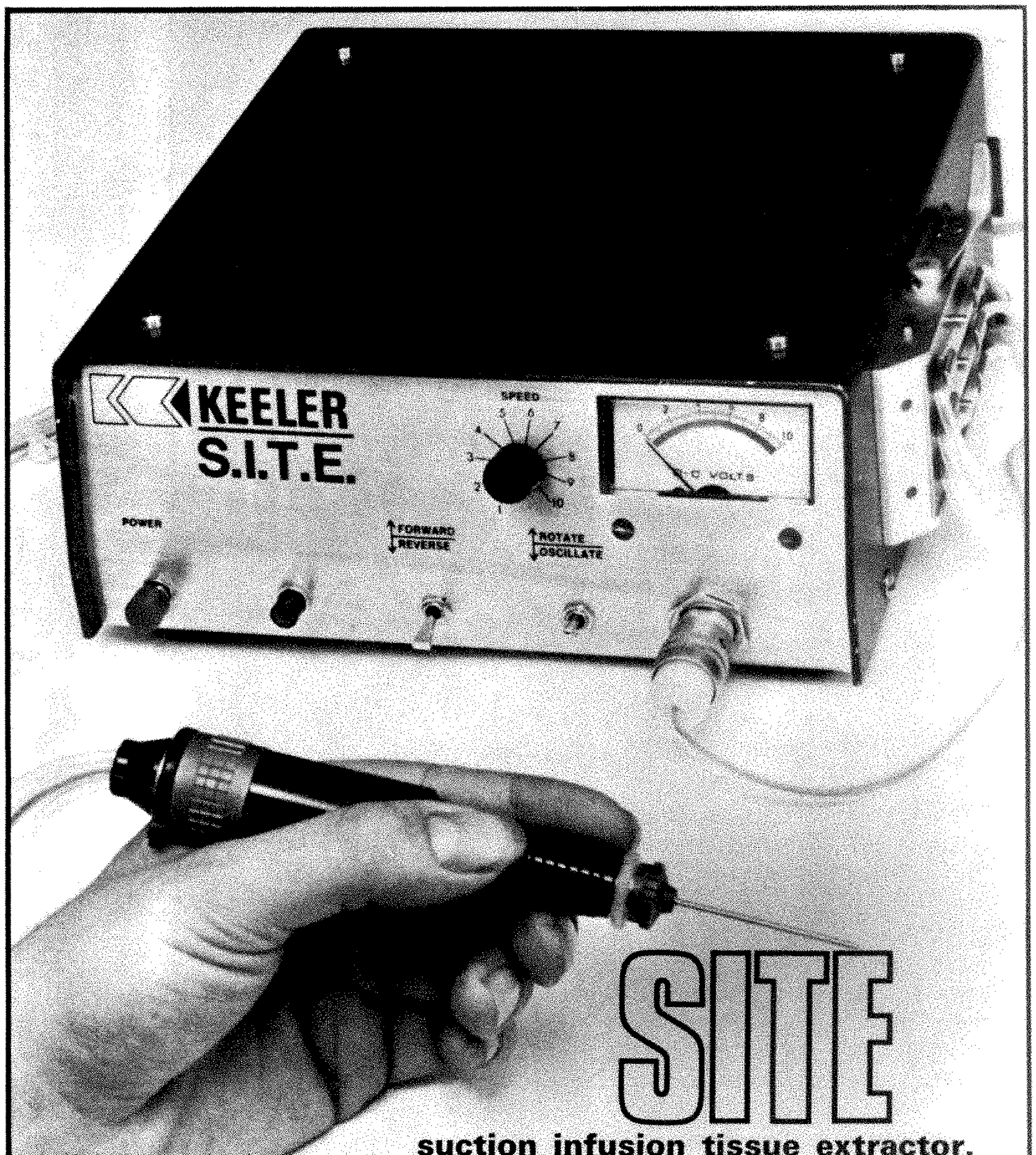

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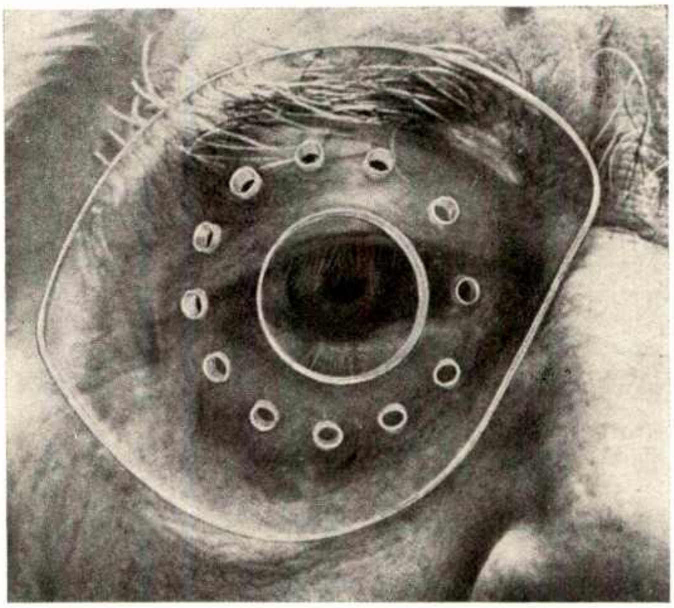

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References: Phillpotts, J. S. Transactions of the O.S.U.K. 1968.
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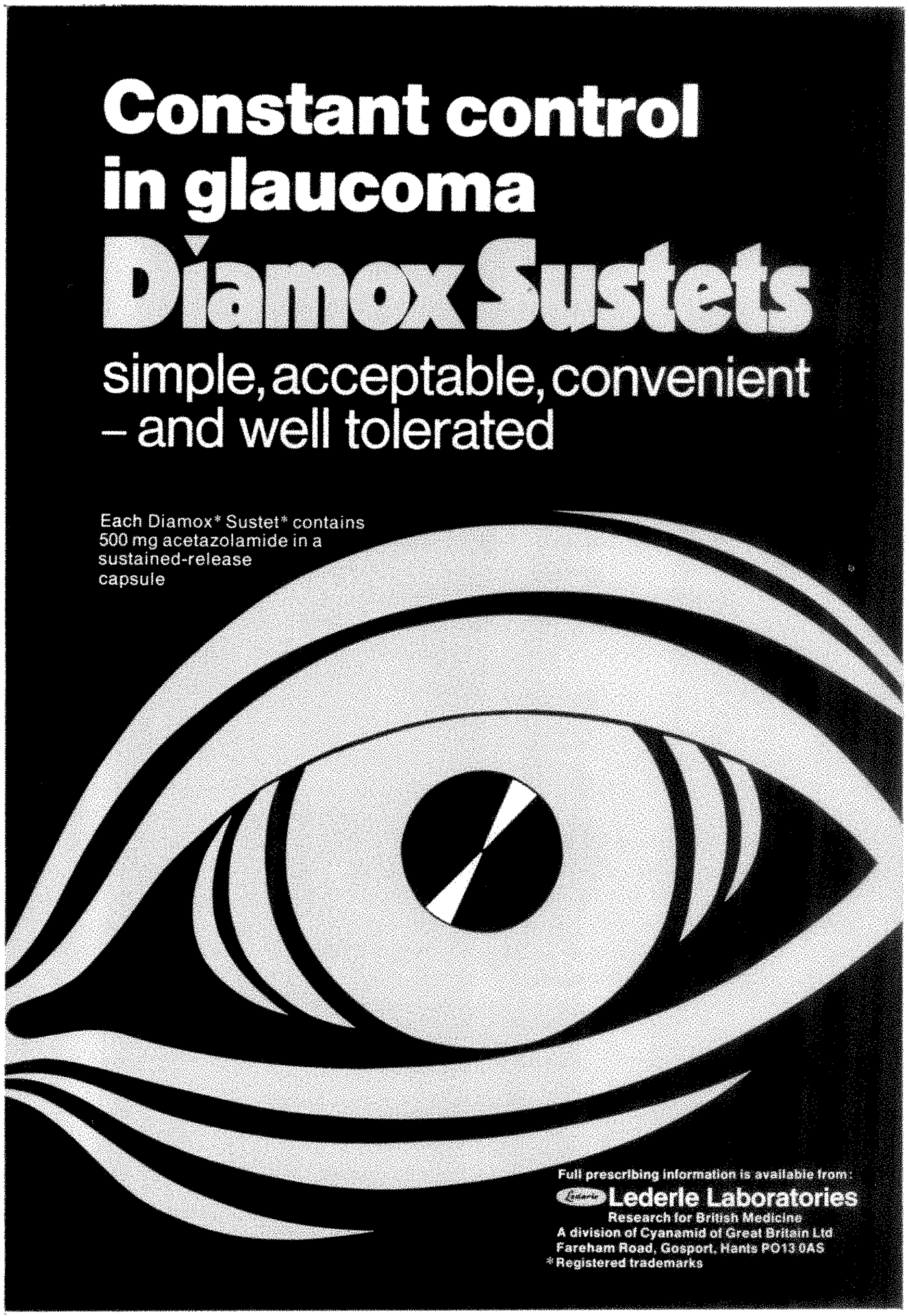

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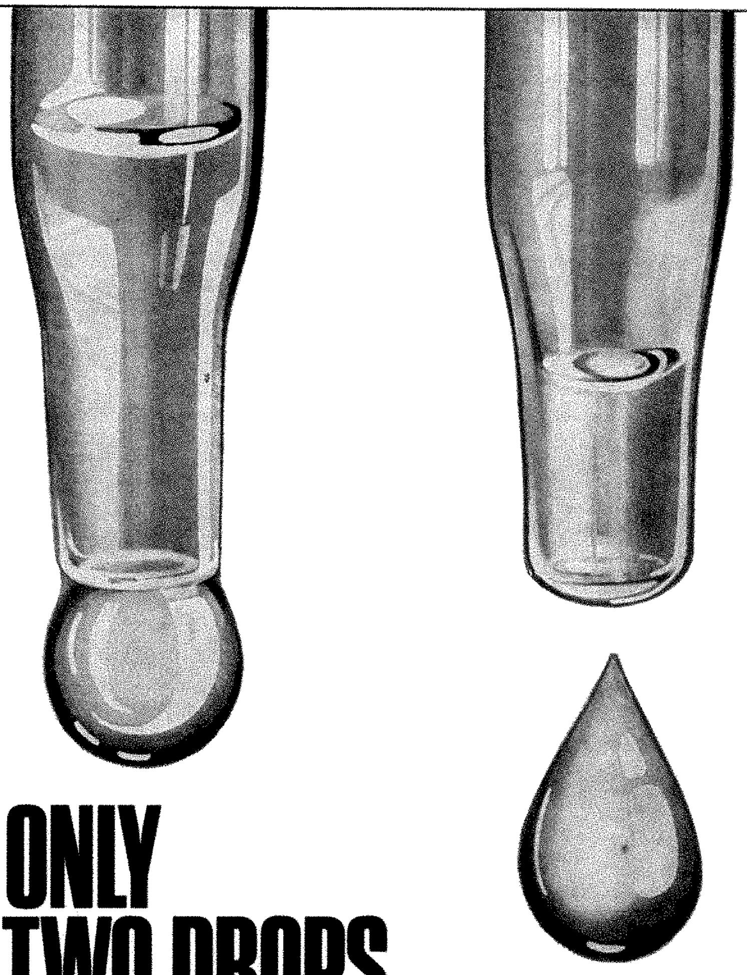

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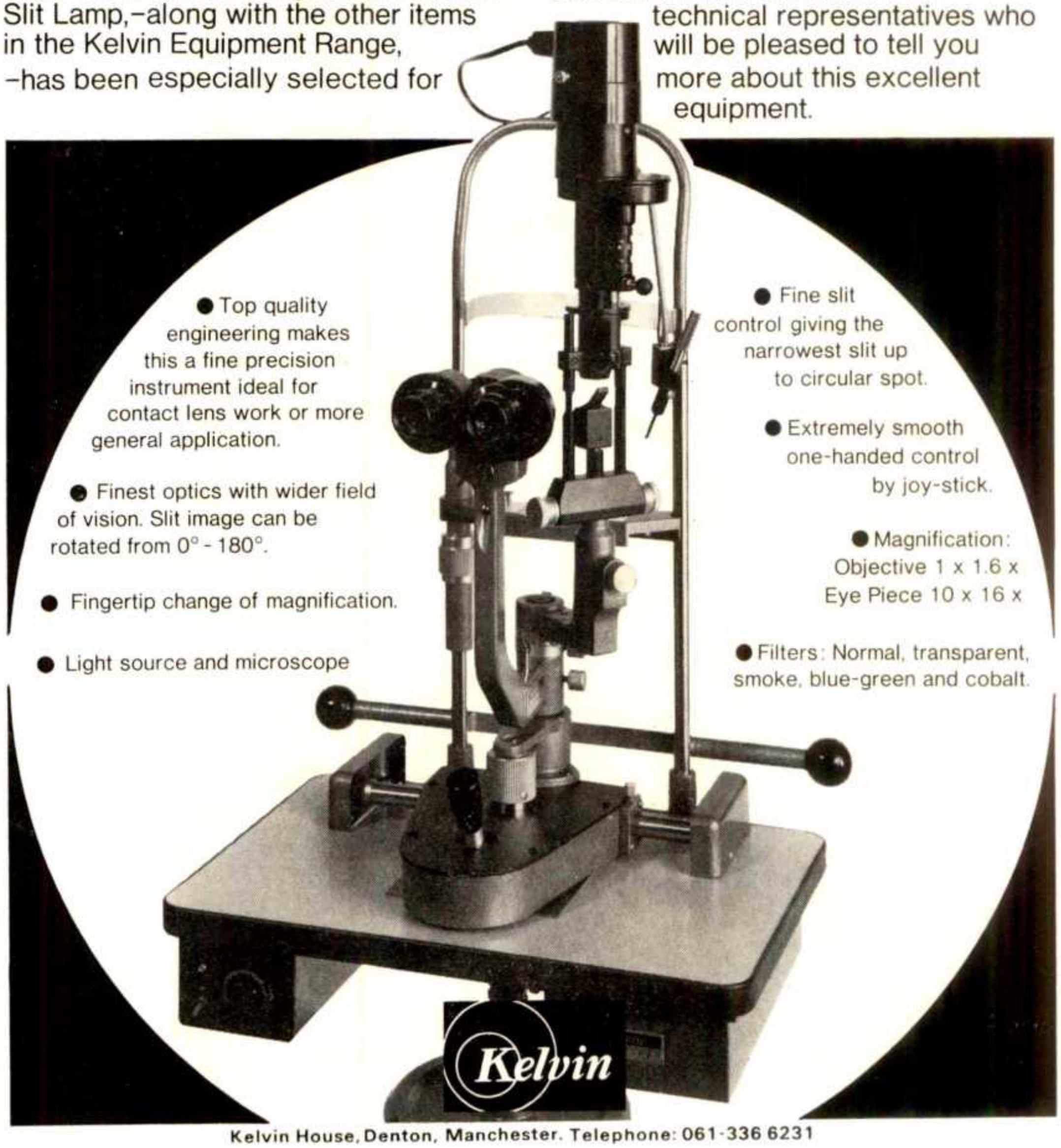

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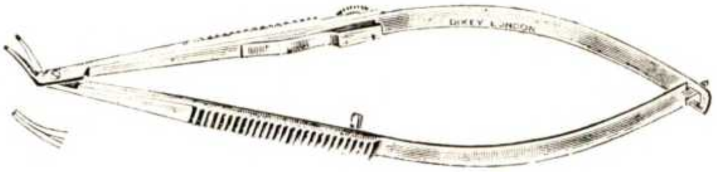

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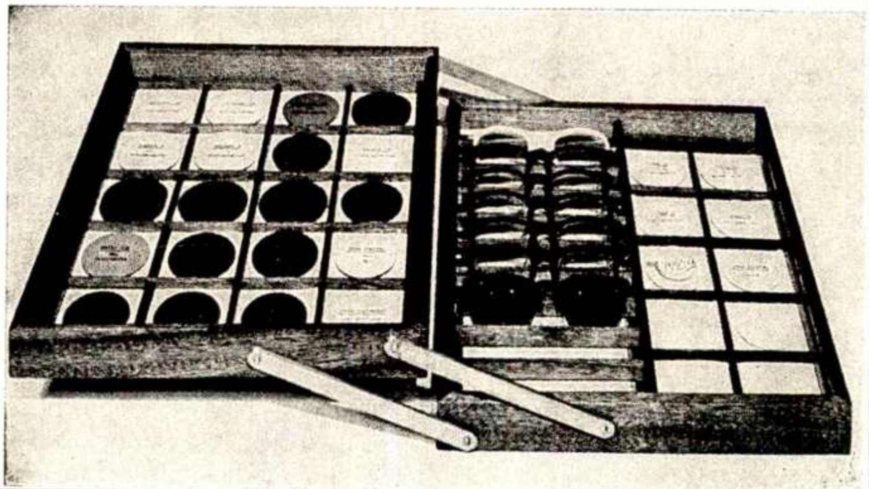

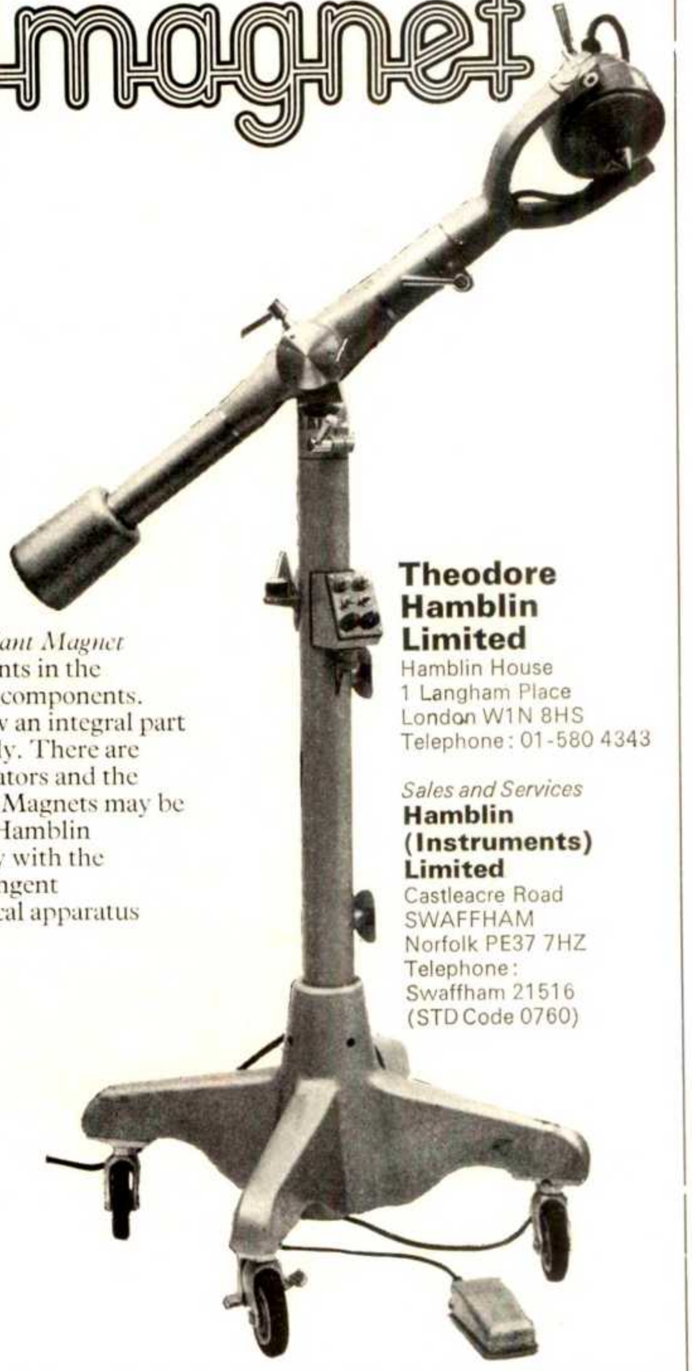

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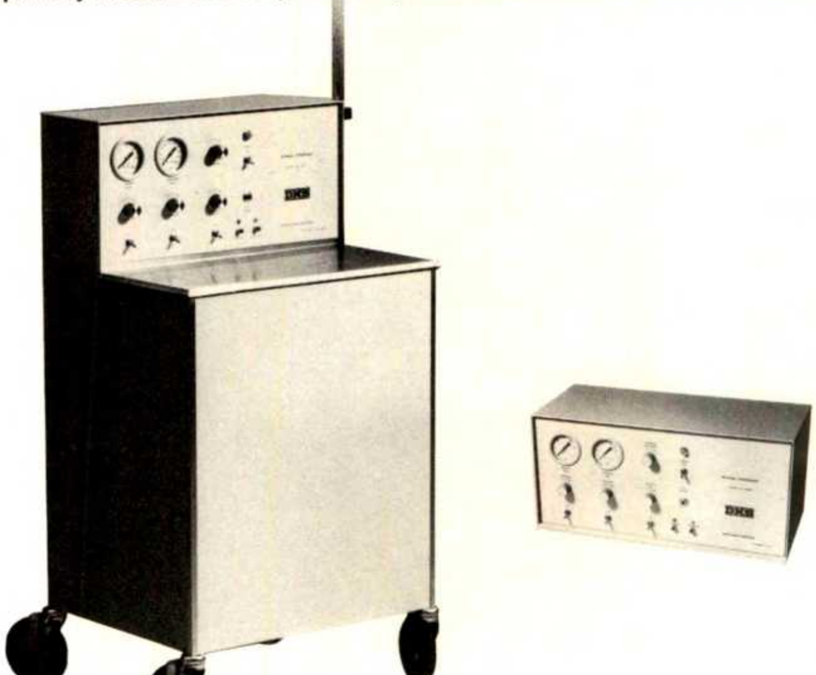

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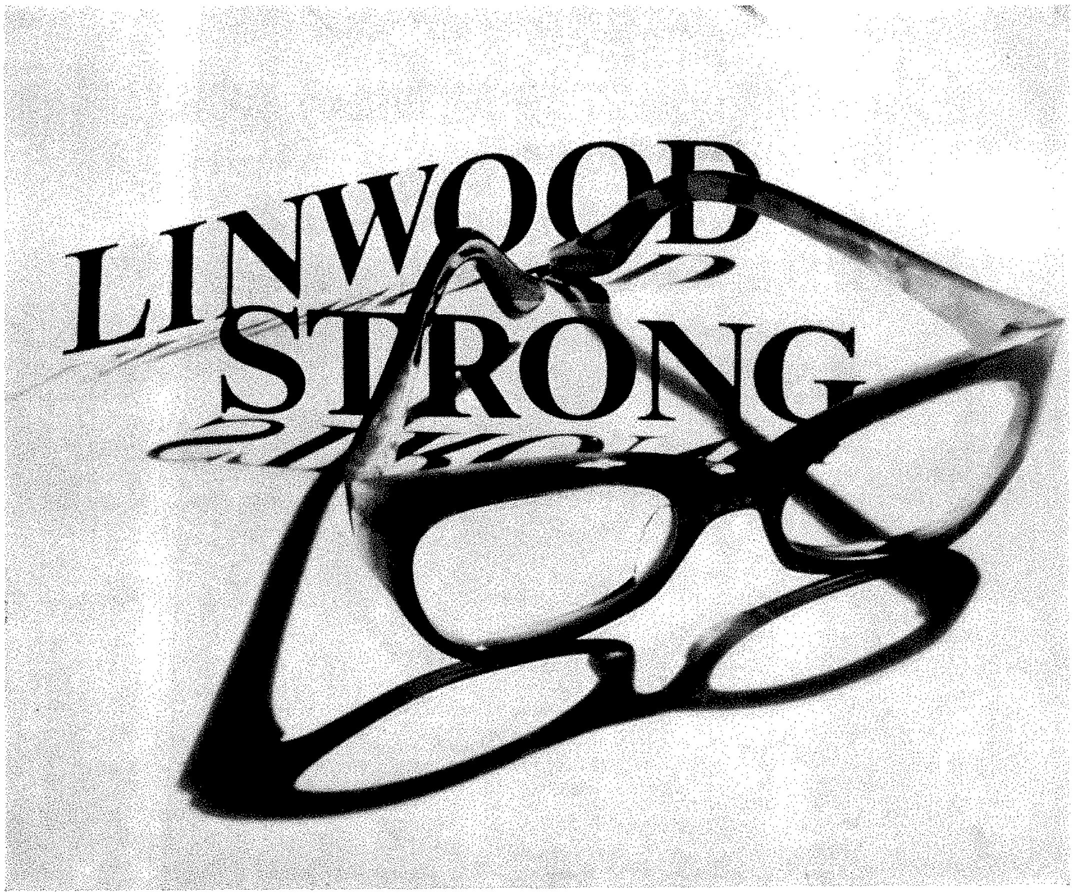

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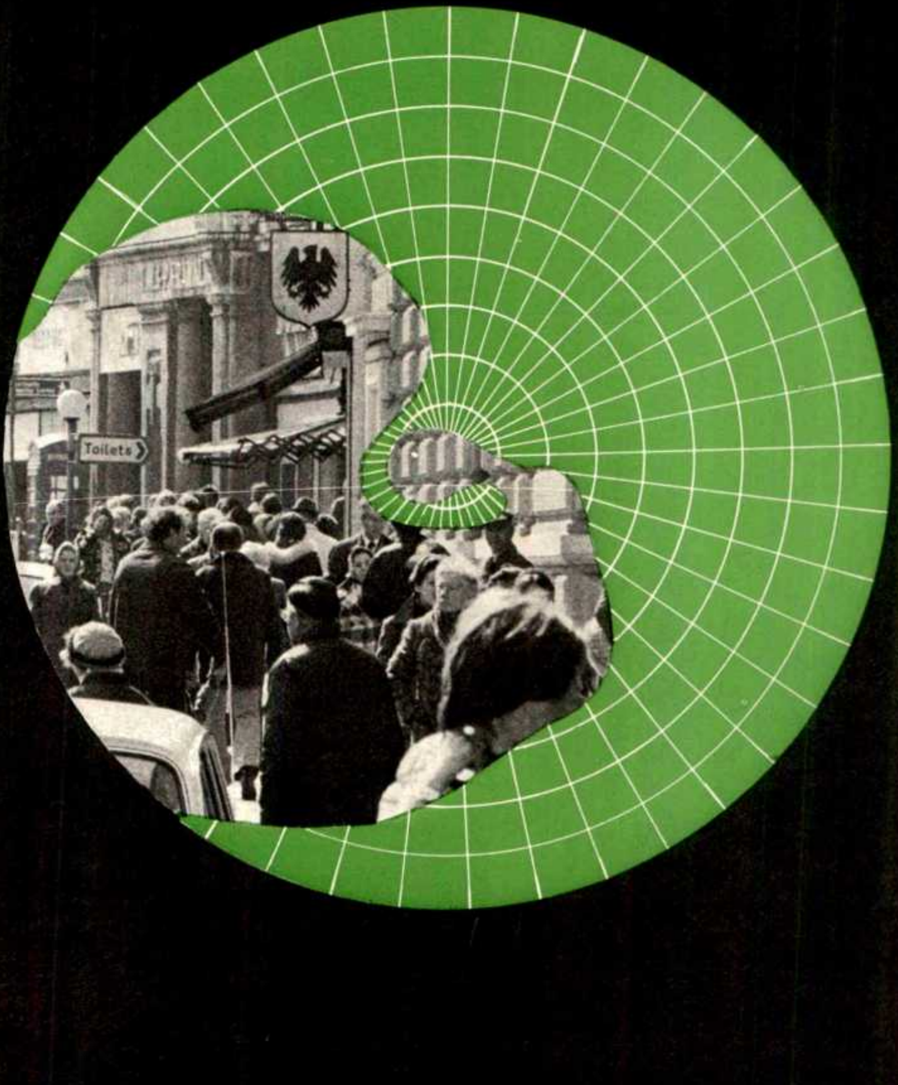

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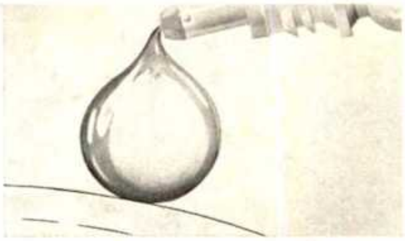

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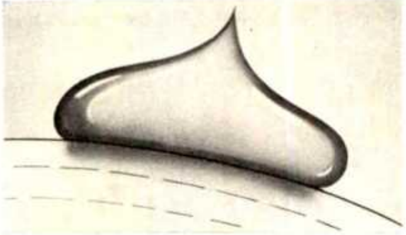

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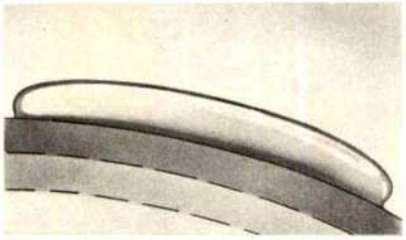

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Congenital duplication of the lens

R. H. B. GREY AND N. S. C. RICE
From Moorfields Eye Hospital, City Road, London

Congenital anomalies of the formation of the lens from the lens plate or lens vesicle are rare and it would seem that reduplication is exceptionally uncommon.

Duplication of the nucleus and cortex within one lens capsule has been recorded on several occasions (Von Graefe, 1854; Erwin, 1894; Clegg, 1914; Marquez, 1922). Although Erwin's case also had glaucoma none of these cases had any other abnormality of the eyes and the condition was unsuspected until the patients underwent cataract extraction. The operations were performed when the patients were aged between 57 and 73 years and were described as uneventful but, after removal of the lens nucleus, a second nucleus was subsequently expressed. These cases would seem not to have been true lens duplications. Von Szily (1938) in the Doyne Memorial Lecture demonstrated the mechanism of the origin of these duplicated nuclei and pointed out that in some areas the epithelium extended posteriorly behind the equator of the lens, thus leading to an irregular arrangement of lens fibres and to two nuclei and cortices, one in front of the other.

Logetschnikow (1893) described a case of a 48-year-old woman on whom he performed a cataract extraction. He noted a large temporal lens and a small nasal lens as opposed to two nuclei separated by a coronal split, but this case also appeared to have one capsule.

True duplication of the lens with separate capsules would seem to be uncommon. Richardson (1951) presented a case of a child of 11 months of age in whom there was considerable maldevelopment of the anterior and posterior segments of the eye. A central corneal tumour was present with a coloboma of the iris, ciliary body, and choroid; there were also two lenses. There was mesenchymal tissue extending from the cornea to the iris surface and the retina was attached to the posterior surface of one of the lenses.

Lyford and Roy (1974) published a case report of an eight-year-old girl with absence of one side of the nose, mental retardation, and unilateral ocular defects. There was a bifid upper lid, coloboma of iris, ciliary body, and choroid and duplication of the lens.

This paper describes a case of true duplication of the lens which has features that distinguish it from previously reported cases.

Case report

A White seven-week-old baby boy was brought to an outpatient clinic by his parents. From the time of his birth they had noticed that his left eye seemed enlarged and had an irregularly-shaped pupil. Although the cornea was clear it appeared larger than the right cornea and there was a typical coloboma of the iris. The mother reported a normal pregnancy followed by an uneventful delivery; the birth weight was 7lb 6oz (3·4 kg). There was no family history of ocular abnormality. A diagnosis of congenital glaucoma was suspected and the child was admitted for examination under general anaesthesia.

The left cornea was oval measuring 13 mm in the 45° meridian and 11 mm in the 135° meridian. The structure of the cornea appeared normal, with no splits in Descemet's membrane, and it was transparent (Fig. 1).

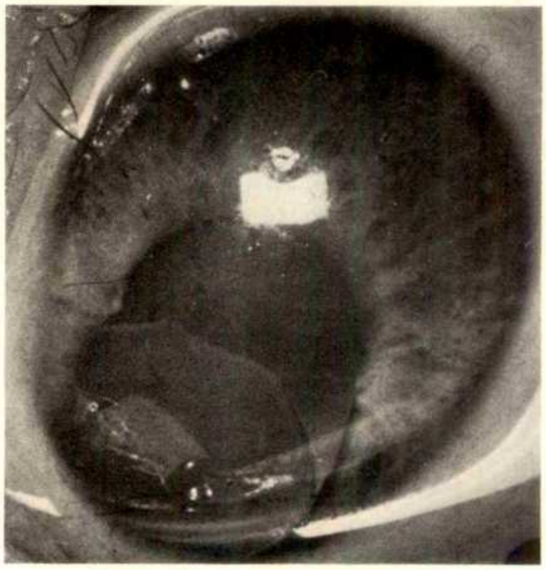

FIG. 1 *Photograph to show oval cornea and iris coloboma*

Address for reprints: R. H. B. Grey, Moorfields Eye Hospital, City Road, London EC1V 2PD

The anterior chamber was of normal depth but the iris had an infero-nasal coloboma involving the whole width of the iris (Fig. 1). Behind the iris there were two well-formed, clear lenses both lying in the coronal plane of the eye. The supero-temporal lens appeared slightly larger than the infero-nasal lens and neither appeared to be dislocated. Both lenses appeared to be circular apart from the upper margin of the inferior lens which had a slightly concave outline (Fig. 2). There was a fine strand stretching from the superior margin of the inferior lens to the nasal edge of the pupil margin and from this point the strand expanded as a thin triangular fibrous sheet on the iris surface reaching the angle of the anterior chamber covering a short area of the trabecular meshwork. Elsewhere the trabecular meshwork appeared normal.

Examination of the fundus showed a coloboma of the choroid with an appearance similar to a drumstick; a thin choroidal defect extended forwards from the disc and expanded in the periphery. There was pigment hypertrophy around the edge of the expanded area, but the retina appeared to be intact over its surface with normal retinal vessels running across it (Fig. 3). The optic disc appeared normal. The intraocular pressure was 16 mmHg. The right eye was normal with a normal refraction.

General examination of the child revealed no other defects and *x*-rays of the head revealed no developmental abnormalities of the nose or skull. The mental development appeared normal and has remained so.

Discussion

During normal embryonic development the lens plate develops in the surface ectoderm in the second week (4 mm stage). This invaginates and forms a pit (5 mm) which then develops into a vesicle by the fourth week (7 mm). Some time before the fifth week (10 mm) the lens vesicle separates from the surface ectoderm and then becomes engulfed in mesodermal tissue. The determinant of these stages of development is the optic vesicle developing from the forebrain. The outer layer of the optic vesicle also acts as the determinant of the development of the choroid.

The case described in this paper showed a typical, partial coloboma of the uvea—that is, in the line of the embryonic cleft and involving only some of the layers of the developing eye. It would seem that there was a mild abnormality arising in the fusion of the outer layer of the optic cup at the 12–13 mm stage which led to the coloboma. Whatever the defect was that prevented this fusion it would seem reasonable to suggest that it had affected, at an earlier stage (5–7 mm), the optic vesicle determining the developing lens plate. Instead of the plate forming a single lens pit and vesicle the defective optic vesicle led to the formation of two lens pits, thus two separate lenses.

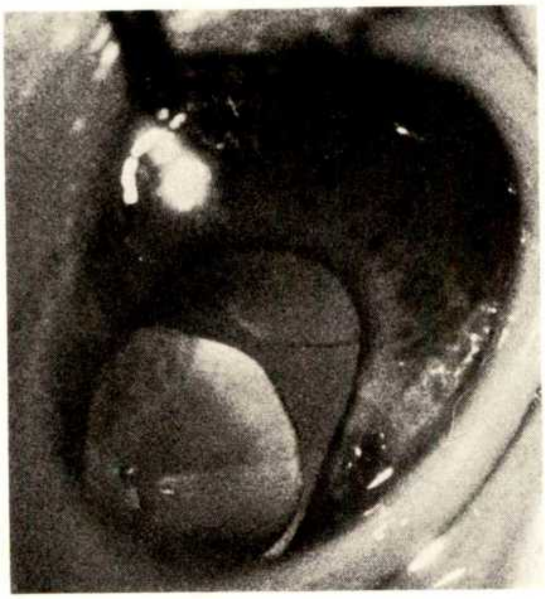

FIG. 2 *Photograph with retroillumination showing iris coloboma and duplicated lens*

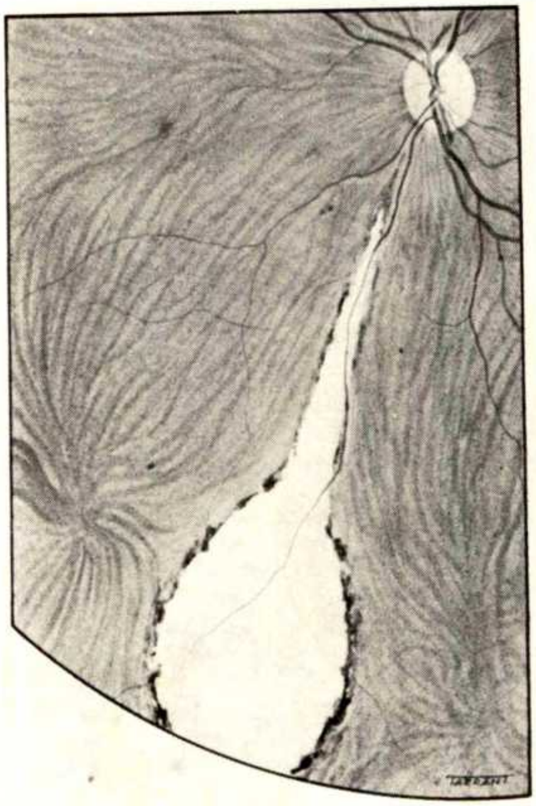

FIG. 3 *Painting of typical partial coloboma of choroid*

In the embryo before the 13 mm stage there are fibrils extending from the lens vesicle to the surface ectoderm—that is, the anterior vitreous. It has been suggested that these fibrils act as the basis for the mesodermal invasion, which later forms the corneal stroma. It would seem probable therefore that if there was an abnormality of the lens vesicle there would be a corresponding abnormality of anterior vitreous fibrils. This could explain the long axis of the oval cornea being in the same meridian as the duplicated lenses in the present case.

Richardson suggested that an abnormality of the central lens plate had led to the formation of two lens vesicles but this would not explain the development of a coloboma, which seems to be present whenever the lens is reduplicated. Also, unlike Richardson's case the other mesodermal structures of the eye appeared largely unaffected. The zonule of the lenses appeared normal and the iris stroma, corneal stroma, and anterior chamber were normal apart from one fine strand from the inferior lens to the iris border and drainage angle.

The patient of Lyford and Roy had an atypical complete coloboma on the lateral side of the eye with unequal lenses. Presumably in this case the more fundamental defect of the fronto-nasal process had secondarily affected the normal fusion of the optic vesicle leading to abnormal determination of the lens plate.

Summary

A case of reduplication of the lens with uveal coloboma is described. This is a rare condition and, unlike the two previously reported cases, the other ocular structures and adnexae appeared normal.

The authors wish to express their thanks to Mrs W. Pennel for secretarial help and to Mr K. Sehmi for photographic assistance.

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Effect of pilocarpine on visual acuity and on the dimensions of the cornea and anterior chamber

D. POINOOSAWMY, S. NAGASUBRAMANIAN, AND N. A. P. BROWN
From the Department of Experimental Ophthalmology, Institute of Ophthalmology, London

There are many data on the effect of pilocarpine on the anterior chamber, particularly in respect to reduction in intraocular pressure and in anterior chamber depth and miosis, but the effect of pilocarpine on the anterior chamber volume and corneal curvature has not previously been studied. Pilocarpine commonly causes reduced visual acuity which may be partly due to miosis, but in this study reduced visual acuity is shown to be mainly due to a myopic change. The mechanism of the myopic change has not previously been established and it is now shown to be caused by changes in radius of curvature of the lens, similar to changes occurring in accommodation; changes in radius of curvature of the cornea are relatively unimportant.

Pilocarpine reduces the anterior chamber depth (Heim, 1941; Rosengren, 1950; Törnqvist, 1956; Bleeker, 1960; Romano, 1968; Wilkie, Drance, and Schulzer, 1969; Poinoosawmy and Roth, 1974). This effect is probably related to an increase in the sagittal width of the lens as demonstrated by ultrasound (Abramson, 1972; Abramson, Coleman, Forbes, and Franzen, 1972) and is not connected with the reduction in intraocular pressure. In this study the reduction in anterior chamber depth is correlated with the reduction in anterior chamber volume and in the radius of curvature of the lens; these have not hitherto been reported.

Miosis may result in better visual acuity in some patients who are initially ametropic, but reduced visual acuity is the more usual effect of pilocarpine. Visual acuity has been shown to improve if the pupil diameter is reduced to 2·5 mm (Hallden, 1973a and b) and to deteriorate with further reduction below this figure; this deterioration is believed to be due to diffraction. The current study shows that changes in visual acuity result from factors unrelated to miosis.

An increased radius of curvature of the cornea has been shown to occur with a rise in intraocular pressure (Poinoosawmy and Roth, 1974). Reduction in corneal radius is therefore to be anticipated with the reduction in intraocular pressure resulting from pilocarpine, but this has not previously been measured. The present study investigates the effect of pilocarpine on the cornea with pachometry and keratometry.

Materials and methods

SELECTION OF SUBJECTS

Altogether 105 patients of both sexes were selected. They ranged in age from 35 to 70 years and included normal subjects as well as patients with confirmed narrow-angle and chronic simple glaucomas. In all 180 eyes were studied.

Methods

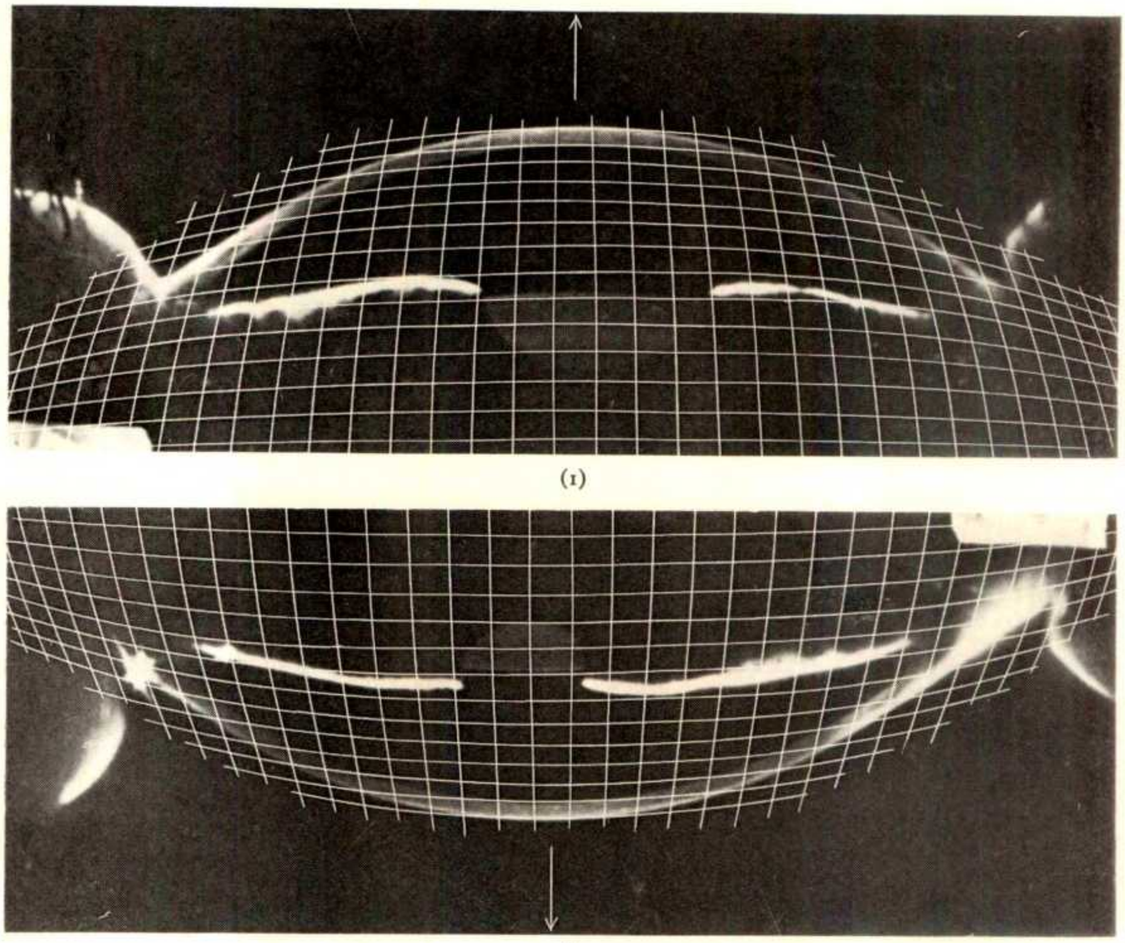
In those patients already receiving pilocarpine, the drug was withdrawn for at least 24 hours before beginning the study. The following parameters were studied before and after the administration of pilocarpine and, in some subjects, again after its withdrawal.

Visual acuity. Standard Snellen chart at 6 m (with distance correction if required).
Anterior chamber depth (Haag-Streit pachometer and slit-image photography).
Anterior chamber cross-section area (slit-image photography, from which anterior chamber volume was calculated).
Corneal thickness (Haag-Streit pachometer).
Applanation tension (Goldmann).
Pupil diameter (pupillometer).
Lens anterior radius (slit-image photography).

The photographic method described by Jones and Maurice (1963) for measuring the volume of the anterior chamber by means of attachments to the Haag-Streit 900 slit-lamp was later modified (Brown, 1973a) to produce an improved image of the anterior chamber; measurements were then made from the photographs using a Perspex grid (Figs 1 and 2). The modified technique was used in the present study for measuring the depth and for calculating the volume of the anterior chamber.

The radius of curvature of the anterior surface of the lens was measured in only 10 eyes in which the lens was sufficiently well recorded in the photographs when the pupil was miosed. The radii were measured from the projected images using the mirror technique as

Address for reprints: D. Poinoosawmy, Department of Experimental Ophthalmology, Institute of Ophthalmology, Judd Street, London WC1H 9QS


(1)

(2)

FIGS 1 and 2 *Anterior segment photographs taken before (Fig. 1) and after (Fig. 2) pilocarpine. Note distance between posterior surface of cornea and anterior surface of lens (3·1 mm before and 2·7 mm after administration)*

described by Fisher (1971) and modified by Brown (1973a) to allow for corneal refraction.

Results

CHANGES IN CORNEA, INTRAOCULAR PRESSURE, AND ANTERIOR CHAMBER DEPTH WITH PILOCARPINE (TABLE I)

There was no change in corneal thickness, but there was a significant reduction in the radii of curvature of both the horizontal and vertical meridia of the corneae with pilocarpine, which correlated well with the reduction in intraocular pressure ($r = 0·64$). There was also a significant shallowing of the anterior chamber.

CHANGES IN VISUAL ACUITY WITH PILOCARPINE

The visual acuity with pilocarpine in 102 glaucomatous eyes deteriorated in 78 eyes, improved in six, and was

Table I *Changes in cornea, intraocular pressure, and anterior chamber depth with pilocarpine*

	Mean values from 55 eyes with glaucoma		
	Without pilo-carpine	*With pilo-carpine*	*Difference*
Corneal thickness (mm)	0·56	0·56	0
Horizontal meridia (mm)	7·86	7·78	−0·08*
Vertical meridia (mm)	7·90	7·81	−0·09*
Intraocular pressure (mmHg)	30·7	19·6	−11·1*
AC depth (mm)	2·72	2·61	−0·11*

*Significant P = > 0·05

unchanged in the remainder. In those eyes in which the visual acuity deteriorated it fell from one to five lines on the Snellen chart. In all these eyes the visual acuity could be corrected to the previous value with the addition of minus spheres to the distance refraction. The correction needed varied from −0·25D to −1·75D with a mean value of 0·95D. Miosis occurred in all eyes but was evidently not the cause of the reduced visual acuity since this could be corrected with minus lenses.

CHANGES IN ANTERIOR CHAMBER DIMENSIONS WITH PILOCARPINE (Table II)

There was a highly significant reduction in anterior chamber depth, area, and calculated volume within 15 minutes (P = < 0·01); this increased up to 30 minutes, but it did not increase after 60 minutes. The anterior chamber volume was found to be well correlated with the anterior chamber depth as shown in Fig. 3.

CHANGES IN LENS RADIUS OF CURVATURE (Table III)

In all the lenses measured, the radius of curvature of the anterior surface became shorter with pilocarpine. The change in radius was highly significantly correlated (r = 0·84) with the degree of myopic change in refraction. The change in radius was also highly significantly correlated (r = 0·84) with the change in anterior chamber depth and inversely r = 0·84 with the age of the subject.

Table II *Changes in anterior chamber dimensions with pilocarpine*

	Mean values for 125 eyes			
	Without pilo-carpine	*After pilocarpine*		
		15 min	*30 min*	*60 min*
AC depth (mm)	2·82	2·38	2·27	2·25
Area (mm²)	21·0	16·5	15·8	15·7
Volume (µl)	155	117	112	111

Table III *Radius of curvature of the anterior lens surface before and after pilocarpine*

	Age (years)	*Before pilocarpine (mm)*	*After pilocarpine (mm)*
1	73	12·5	9·3
2	39	14·8	9·3
3	68	13·5	10·9
4	74	11·2	10·6
5	45	12·7	9·7
6	73	10·1	8·1
7	77	12·8	9·4
8	75	11·8	11·0
9	65	13·8	9·4
10	68	11·9	8·2

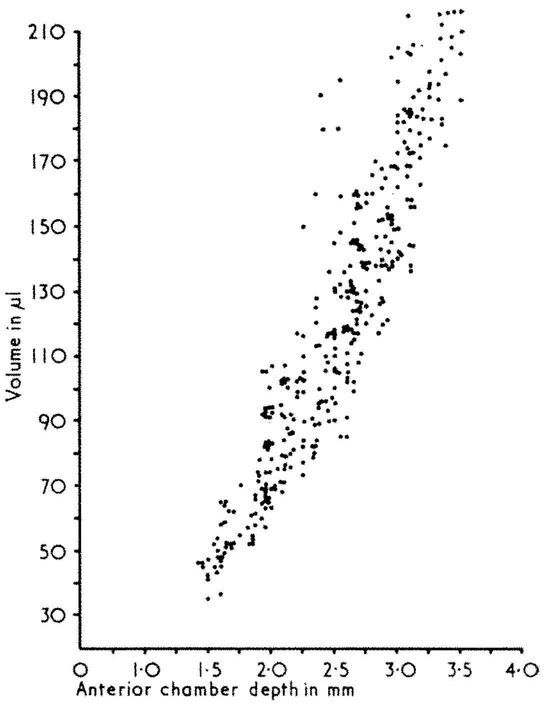


FIG. 3 *Correlation between volume and depth of anterior chamber*

Discussion

This decrease in the depth of the anterior chamber as a result of pilocarpine confirms earlier reports (Heim, 1941; Rosengren, 1950; Törnqvist, 1956; Bleeker, 1960; Abramson and others, 1972).

The change in visual acuity for distance appears to be accounted for by a myopic shift since the visual acuity could be corrected to pretreatment levels, in all patients in whom it was reduced, by the addition of minus lenses.

The small reduction in radius of curvature of the cornea after pilocarpine had been instilled is likely to be related directly to the fall in intraocular pressure. The reduction in radius alone would produce a myopic shift, but it is likely to be outweighed by an accompanying reduction in axial length of the globe. It has previously been shown (Poinoosawmy and Roth, 1974) that raised intraocular pressure is associated with an increase in the radius of curvature of the cornea and with a myopic shift which appears to be due to increased axial length of the globe. Thus the small changes in external dimensions of the eye resulting from reduced intraocular pressure would probably result in a net hypermetropic shift. But since the overall change is towards myopia, the changes in the axial length must be outweighed by other changes in the eye and it is likely that changes in the lens are responsible. A forward movement of the anterior pole of the lens is demonstrated in all subjects in whom there is a myopic shift and 10 of these subjects in whom the radius of curvature of the anterior lens surface could be measured showed a reduction in radius. The present study does not measure the sagittal width of the position of the posterior pole of the lens.

It seems likely that the changes now observed in the lens of the eyes are the same as those occurring in accommodation in which the increase in sagittal width of the lens is associated with a greater forward movement of the anterior pole than backward movement of the posterior pole, so that there is a forward movement of the lens centre (Coleman, 1970; Brown, 1973b). Similar changes have also been demonstrated by ultrasound after pilocarpine administration (Abramson, 1972).

Forward movement of the lens increases its effectiveness, but in accommodation it is mainly the change in lens radius of curvature which is responsible for producing near focus (Brown, 1973b). It is likely that the reduced radius of curvature of the lens is the main factor in producing myopia in our subjects.

It appears that the myopia induced by pilocarpine is due to the action on the ciliary body causing it to contract and to produce the lens changes normally seen in accommodation. The myopic changes were least in the older subjects as could be expected from the presbyopic reduction in accommodation.

Another interesting observation in the present study is the correlation between the depth and volume of the anterior chamber, which was found to be highly significant. Jones and Maurice (1966) obtained a value of 175±30 μl for the volume of the anterior chamber in normal subjects. The mean volume in the pretreated group in our study, which included both normal and glaucomatous eyes, was approximately 154·62±7·0221 μl, and the slight difference could well be due to the inclusion of eyes with shallow anterior chambers.

Summary

The effect of pilocarpine on visual acuity and on the dimensions of the cornea, anterior chamber, and lens were studied in two groups of subjects. Significant changes in ocular tension, corneal curvature, anterior chamber depth, and lens anterior radius were found in a group of 55 glaucomatous eyes as a result of pilocarpine treatment, but there was no change in corneal thickness. Out of 102 glaucomatous eyes 78 became relatively myopic, and this appears to be due to changes in the dimensions of the lens of the eye similar to those occurring in accommodation, as a result of the effect of the drug on the ciliary muscle.

The effect of pilocarpine on anterior chamber depth, area, and volume was studied in 125 eyes using a photographic method, and a significant reduction in the dimensions of the anterior chamber was observed as a result of the administration of pilocarpine. A significant correlation between depth and volume was also noted and the implications of this are discussed.

We thank Professor J. Gloster for allowing us to examine his patients in the Glaucoma Clinic of the Institute of Ophthalmology and Professor E. S. Perkins for useful discussions.

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Early dose response analysis of ocular hypotensive effects of propranolol in patients with ocular hypertension

KARIN WETTRELL AND MAURIZIO PANDOLFI
From the Department of Ophthalmology, Hospital of Malmö,
University of Lund, Sweden

Cumulative evidence indicates that propranolol (Inderal®), a β-adrenergic antagonist blocking both β_1 and β_2 receptors, decreases the intraocular pressure (IOP). This substance has been administered topically (Musini, Fabbri, Bergamaschi, Mandelli, and Shanks, 1971; Bietti, 1972; Vale, Gibbs, and Phillips, 1972), intravenously (Phillips, Howitt, and Rowlands, 1967; Vale and Phillips, 1970; Sharaf, Haroun, Ishaac, Shewy, and Nassef, 1974), and orally (Phillips and others, 1967; Coté and Drance, 1968; Öhrström, 1973; Pandolfi and Öhrström, 1974; Wettrell and Pandolfi, 1975), both in healthy volunteers and in patients with ocular hypertension or glaucoma. No information is available on the dose-intraocular pressure response to administration of propranolol.

The aim of the present study was to determine the time-course and dose-response of the intraocular pressure of propranolol administered orally to patients with ocular hypertension.

Materials and methods

The trial was performed in a single-blind manner with the patients being unaware of the dose level employed. Two groups each comprising six patients with ocular hypertension were studied. The first group consisted of four women and two men aged between 65 and 69 years with an IOP ranging from 20 to 29 mmHg (Group A). The second group consisted of five women and one man aged between 43 and 69 years with an IOP ranging from 30 to 39 mmHg (Group B). At 8 a.m. on the first day of the trial two people in Group A were found to have one single IOP value exceeding that for the group (one had an IOP of 30 mmHg, the other 32 mmHg) but as in neither case was this later observed to rise above 30 mmHg, these persons were included in Group A. All previous treatment, ocular or otherwise, was stopped at least 24 hours before the beginning of the trial. On the initial visit the patients were questioned on previous history of asthma, brochospasm, or other states contraindicating adrenergic beta-blockers. Cardiovascular examination was performed and electrocardiograms taken to ascertain their suitability for the study.

Propranolol or placebo was administered orally in a single dose at 9 a.m. after fasting 12 hours. Two hours later, a light lunch was served. Placebo and propranolol in doses of 20, 40, and 80 mg were tested at intervals of at least 48 hours.

One hour before and each hour after administration of propranolol or placebo the IOP was tested using a Goldmann applanation tonometer. After some rest in supine position the systemic blood pressure and pulse rate were recorded hourly. The tonometer was calibrated daily and the systemic blood pressure was measured with a sphygomanometer which had previously been tested at the local department of medicine.

All results were expressed as the arithmetic mean ± the standard error of the mean. The method of least squares (least square line) was used to obtain the dose-response curve. The significance of differences was calculated by Student's *t* test.

Results

In both groups a decrease in mean IOP was noted after one hour, reaching its maximum after three hours. The decrease in IOP showed a clear dose-correlation (Tables I and II; Figs 1 and 2). The maximum mean IOP reduction after 20, 40, and 80 mg propranolol in Group A was 6·2, 6·9, and 8·5 mmHg, respectively. In Group B the corresponding decrease was 5·8, 7·8, and 9·8 mmHg. A similar decrease in mean IOP was also found in the fellow eye. Six hours after administration of propranolol the mean IOP in both groups was still reduced, the reduction still being proportional to the dose administered.

The mean systolic blood pressure decrease was only moderate (Table III). The maximum fall was observed between three and four hours after administration of 20, 40, and 80 mg propranolol; in Group A it was 10, 25, and 15 mmHg, and in Group B 13, 15, and 16 mmHg, respectively. The reduction showed no obvious dose-relationship and was never statistically significant with one exception (40 mg propranolol three hours after administration). The absolute fall in mean diastolic pressure was even slighter and did not exceed 10 mmHg for any dose level studied. Statistical significance was never attained.

The decrease in pulse rate was appreciable one hour after administration of propranolol and

Address for reprints: Karin Wettrell, MD, Department of Ophthalmology, Hospital of Malmö, University of Lund, 214 01 Malmö, Sweden

Table I *The time-course of the IOP response of six ocular hypertensive patients (20 to 29 mmHg) after treatment with placebo and different doses of propranolol*

Initial highest IOP *Dosage*	*Hours* −1	 0	 1	 2	 3	 4	 6
Placebo	27·3 ±1·26	25·5 ±1·02	24·2 ±0·95	23·5 ±1·26	23·2 ±1·56	24·5 ±1·09	24·3 ±0·61
20 mg	24·7 ±1·15	24·3 ±0·76	20·8* ±0·60	18·3† ±0·42	17·0† ±1·00	19·3† ±0·56	22·0 ±1·53
40 mg	25·7 ±1·09	24·5 ±0·62	20·2* ±1·19	17·0† ±0·68	16·3† ±0·80	17·5‡ ±0·50	19·3† ±1·02
80 mg	26·0 ±0·58	24·8 ±0·98	16·7‡ ±0·71	15·3‡ ±0·67	14·7‡ ±0·33	15·3‡ ±0·99	17·0‡ ±1·29
Fellow eye Placebo	23·8 ±1·25	21·8 ±1·11	20·5 ±1·18	20·7 ±1·20	20·3 ±1·33	20·8 ±0·91	22·7 ±1·54
20 mg	21·8 ±0·60	21·5 ±0·76	19·2 ±0·60	17·5* ±0·43	17·0 ±0·93	17·3† ±0·21	19·5 ±0·67
40 mg	21·7 ±0·61	21·3 ±0·71	18·0 ±1·03	16·8* ±0·65	15·3† ±0·80	16·0† ±0·86	17·8* ±0·87
80 mg	21·7 ±0·42	21·7 ±1·15	15·7* ±1·20	14·0† ±1·03	13·7† ±0·92	14·7‡ ±0·92	15·3† ±1·02

Values expressed as mean ±SEM (mmHg). Statistical significance expressed as *(P <0·05); †(P <0·01); ‡P <0·001)

Table II *The time-course of the IOP response of six ocular hypertensive patients (30 to 39 mmHg) after treatment with placebo and different doses of propranolol*

Initial highest IOP *Dosage*	*Hours* −1	 0	 1	 2	 3	 4	 6
Placebo	32·2 ±0·98	31·3 ±0·71	28·5 ±0·99	29·5 ±1·48	28·0 ±1·10	27·7 ±1·15	30·2 ±1·54
20 mg	32·2 ±1·28	31·8 ±1·94	29·3 ±1·61	23·2† ±1·19	22·2* ±1·62	25·8 ±1·25	26·0* ±0·68
40 mg	33·5 ±1·18	30·8 ±1·70	24·8 ±1·35	22·0† ±1·03	20·2‡ ±1·05	21·5† ±1·38	25·0* ±1·67
80 mg	32·0 ±1·24	32·3 ±1·71	23·8* ±1·82	19·0‡ ±0·93	18·2‡ ±0·79	19·2‡ ±0·95	21·0‡ ±0·77
Fellow eye Placebo	30·7 ±0·88	29·3 ±0·80	26·8 ±0·79	26·7 ±0·84	26·8 ±0·79	26·2 ±1·19	26·8 ±1·14
20 mg	30·5 ±0·92	30·2 ±0·70	26·8 ±1·01	22·7* ±1·15	21·8† ±1·19	24·2 ±1·05	25·0 ±0·45
40 mg	30·5 ±0·72	28·8 ±0·79	21·0† ±1·00	20·3‡ ±1·02	19·0‡ ±0·77	20·0* ±1·55	22·8* ±1·25
80 mg	29·7 ±0·84	29·7 ±1·41	22·7 ±1·74	18·5‡ ±1·06	17·2‡ ±1·14	18·7‡ ±1·05	19·5‡ ±0·85

Values expressed as mean ±SEM (mmHg). Statistical significance expressed as *(P <0·05); †(P <0·01); ‡(P <0·001)

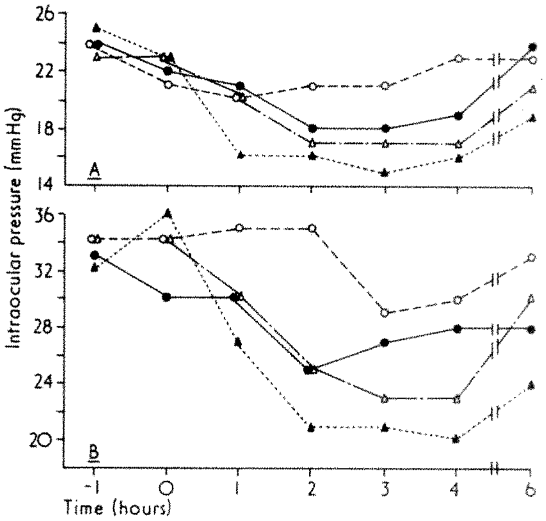

FIG. 1 *The time course of the IOP response in two cases, one from each pressure group, recorded from the eye with the highest IOP after treatment with placebo and different doses of propranolol. The substances were administered at T = 0 hour*
Placebo (○——○), *20 mg propranolol* (●——●), *40 mg propranolol* (△——△), *80 mg propranolol* (▲——▲).
(A) *Initial highest IOP ranging 20 to 29 mmHg.*
(B) *Initial highest IOP ranging 30 to 39 mmHg*

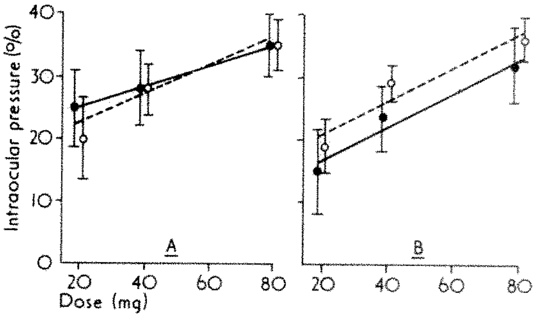

FIG. 2 *Mean maximum IOP decrease ± SEM in per cent after administration of different doses of propranolol*
Initial highest IOP ranging 20 to 29 mmHg (●——●).
Initial highest IOP ranging 30 to 39 mmHg (○ - - - - ○).
(A) *Eye with the highest IOP.* (B) *Fellow eye*

reached its maximum after two hours. The fall in pulse rate showed a clear correlation with the doses given (Table IV).

Differences were statistically significant at doses of 40 and 80 mg.

Discussion

The results of the present study indicate that orally-administered propranolol causes a statistically

Table III *The time-course of the systolic blood pressure response of 12 ocular hypertensive patients after treatment with placebo and different doses of propranolol*

Initial highest IOP (mmHg)	*Dosage*	*Hours* 0	 1	 3	 6
20–29	Placebo	171 ±5·23	166 ±5·39	168 ±6·29	167 ±6·01
	20 mg	161 ±3·27	155 ±3·42	158 ±5·59	161 ±6·38
	40 mg	155 ±5·48	153 ±4·41	143† ±3·59	159 ±6·88
	80 mg	159 ±8·60	160 ±5·16	153 ±6·29	156 ±8·70
30–39	Placebo	158 ±6·67	158 ±8·63	153 ±6·16	149 ±6·76
	20 mg	151 ±8·41	150 ±8·56	140 ±7·53	144 ±8·60
	40 mg	152 ±9·37	142 ±8·63	138 ±9·01	151 ±9·08
	80 mg	156 ±6·88	149 ±7·24	145 ±7·53	148 ±11·24

Values expressed as mean ± SEM (mmHg). Statistical significance expressed as †(P<0·01)

Table IV *The time-course of the decrease in pulse rate of 12 ocular hypertensive patients after treatment with placebo and different doses of propranolol*

Initial highest IOP (mmHg)	*Dosage*	*Hours* 0	 1	 2	 4	 6
20–29	Placebo	68·3 ±4·57	68·7 ±4·70	67·7 ±4·18	68·7 ±4·86	71·3 ±3·99
	20 mg	62·3 ±2·60	58·7 ±3·45	59·0 ±3·42	59·3 ±3·53	61·3 ±3·25
	40 mg	61·7 ±2·85	57·0 ±3·49	55·0* ±3·00	60·3 ±3·07	62·7 ±3·37
	80 mg	63·0 ±3·53	55·7* ±2·99	53·3* ±2·81	58·3 ±4·05	61·3 ±3·64
30–39	Placebo	80·0 ±5·24	79·0 ±5·63	74·7 ±5·43	78·7 ±4·34	80·0 ±3·76
	20 mg	70·3 ±3·28	67·0 ±3·68	63·3 ±1·91	69·0 ±4·09	72·0 ±3·22
	40 mg	71·7 ±5·67	65·0 ±4·19	59·3* ±4·22	65·7 ±3·91	69·0 ±4·49
	80 mg	73·3 ±5·10	59·3† ±0·84	59·3* ±2·56	64·0* ±3·54	66·0* ±4·23

Values expressed as mean ±SEM (beats/min). Statistical significance expressed as *(P<0·05); †(P<0·01)

significant decrease of IOP in intraocular hypertensive patients which is clearly dose-dependent. The reduction was appreciable one hour after administration and reached its maximum after three hours at all dose levels tested. It was still present six hours after the administration. This is in agreement with the recently published study by Cuthbert and Collins (1975) in which the plasma level after a single oral dose of propranolol (40 mg) was at its highest after two to three hours. Also the maximum degree of beta-adrenoreceptor blockade as judged from the effect on the pulse rate (isoprenaline ratio) was observed at approximately the same time. However, orally-administered propranolol undergoes hepatic metabolism with conversion of drug to active metabolites (Fitzgerald and O'Donnel, 1971) and, therefore, the drug plasma level may not reflect the total beta-inhibitory effect of the substance. Topically applied propranolol is able to bring about a decrease in IOP which is noticeable after one hour and has maximum effect after two to three hours (Vale and others, 1972). Similar time course of IOP response after intravenous administration in man was reported by Vale and Phillips (1970) although no obvious dose-relationship could be demonstrated in these experiments; this discrepancy was explained by the fact that two different doses (1 and 4 mg) of propranolol were used and administered at short intervals so when the second and largest dose was given the intraocular pressure was already reduced and, therefore, a further decrease proportional to this dose was difficult to achieve.

In agreement with Coté and Drance (1968) we found an evident reduction of IOP after even the smallest dose (20 mg) in both the groups. Noteworthy was the fact that the absolute mean IOP fall during treatment with similar doses of propranolol was greater in the group with higher initial IOP, a finding also reported by Coté and Drance (1968).

The decrease in systolic and diastolic blood pressure was only moderate and never attained statistical significance with one exception. Nor was any dose-relationship demonstrated.

The simultaneous recording of heart rate in the supine position showed during treatment a decrease which was significant in both the groups for the doses of 40 and 80 mg. The mean maximum fall was shown to be after one to two hours with an obvious dose-dependence.

The virtual absence of a significant decrease in blood pressure and the lack of correlation with the doses administered suggests that the fall in blood pressure is not the primary cause of the reduced IOP.

Summary

Placebo and propranolol (Inderal®) in doses of 20, 40, and 80 mg were given in a single-blind test to two groups of six ocular hypertensives. The groups

consisted of patients with an intraocular pressure ranging from 20 to 29 mmHg and 30 to 39 mmHg. The doses were given 48 hours apart and administered after fasting 12 hours. IOP by Goldmann applanation tonometer, systemic blood pressure and pulse rate in the supine position were recorded hourly before and after administration. In both groups a decrease in mean IOP was noted after one hour and this reduction reached its maximum three hours after the administration of propranolol. The absolute reduction was greater in the group with the highest initial IOP and in both groups the fall in mean IOP showed a clear dose-dependent correlation. The simultaneous mean decrease in pulse rate was also dose-correlated, but reached its maximum two hours after administration. The fall in systemic blood pressure was only moderate and showed no obvious dose-dependence.

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Practolol and ocular toxicity

Antibodies in serum and tears

A. GARNER AND A. H. S. RAHI
From the Department of Pathology, Institute of Ophthalmology,
University of London, Judd Street, London

The use of practolol, a β-adrenergic receptor blocking agent, in the management of cardiac dysrhythmia and ischaemic heart disease, is associated in a few patients with ocular disturbance (Wright, 1974, 1975; Rahi, Chapman, Garner, and Wright, 1976). Essentially this presents as a painful dry eye with subconjunctival fibrosis and occasional corneal ulceration. The eye lesions are usually associated with skin rash and both are linked with circulating antinuclear factors and antibodies which attach to the membranes of squamous epithelia (Wright, 1975; Rahi and others, 1976; Amos, Brigden, and McKerron, 1975). We here report our antibody findings in the sera and tears of affected patients.

Patients and methods

Twenty-two patients who had developed lesions or symptoms in the outer eye while receiving practolol (Eraldin) were investigated and allocated to one of two groups according to the severity of their condition. Group A consisted of 14 patients whose complaint of a hot, gritty sensation in the eyes was associated with reduced tear secretion and an abnormal conjunctival epithelium as evidenced by positive rose bengal staining. The eight patients in Group B had symptoms but they had few objective signs, or none, of ocular disease. Tear samples were collected either in capillary tubes or on triangular sponges from 15 patients and from 20 healthy individuals. Blood specimens were also obtained from each patient and from 100 control subjects.

Levels of serum immunoglobulins G, A, and M were estimated using a radial immunodiffusion technique (Mancini, Carbonara, and Heremans, 1965). IgM-rheumatoid factor and antithyroid antibodies were demonstrated using diagnostic kits supplied by Burroughs-Wellcome Ltd, while antinuclear and other autoantibodies were identified by standard indirect immunofluorescent techniques at an initial serum dilution of 1 : 10. Immunofluorescent specimens were examined using a Zeiss epifluorescence microscope with an FITC interference filter. The incidence of antibodies in patients and control subjects was compared using the χ^2 test.

Tear immunoglobulins, lysozyme, transferrin, and albumin were demonstrated by immunoelectrophoresis in veronal buffer (pH 8·6, I = 0·075) at a constant current using polyvalent antihuman sera and antisera specific for IgG, IgM, IgA, and the secretory component of IgA. Lysozyme formed a characteristic non-immune precipitate during electrophoresis, the nature of which was confirmed in a few samples by elution and by testing against antilysozyme serum on Ouchterlony plates. In an attempt to quantify the protein levels the immunoelectrophoretic precipitin lines were scored according to their length, intensity, and distance from the antibody-containing trough. Precipitin lines recognizable only after staining with nigrosine were counted as +, while those seen in unstained preparations were scored as either ++ or +++. In a separate study of the IgA content of tears it was found that + represented anti-

Table I *Serum immunoglobulins and autoantibodies in control subjects and in patients with practolol-induced ocular disease*

Category and no. of patients	*Healthy subjects* (100)	*Group A* (14)	*Group B* (8)
IgG (IU/ml)			
mean	121	137	123
range	70–282	98–220	86–163
IgA (IU/ml)			
mean	125	154	118
range	64–300	80–240	78–210
IgM (IU/ml)			
mean	151	142	129
range	67–300	96–269	100–201
Autoantibodies (per cent positive)			
Antinuclear antibody	15	64	25
Antinucleolar antibody	2	Nil	Nil
Smooth muscle antibody	16	28	13
Antibody to gastric parietal cells	3	Nil	Nil
Antireticulin antibody	2	Nil	Nil
Rheumatoid factor (rheumaton test)	9	Nil	Nil
Antithyroglobulin antibody (dilution 1 : 25)	12	14	12

Address for reprints: Dr A. Garner, Department of Pathology, Institute of Ophthalmology, Judd Street, London WC1H 9QS

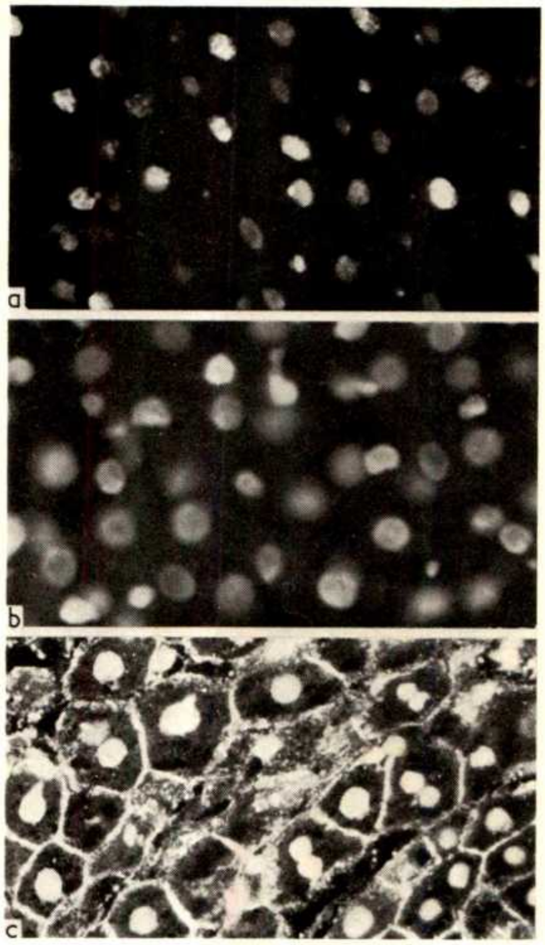

FIG. 1 *Cryostat sections of rat liver pre-incubated with patient's serum and treated with fluorescein-conjugated antihuman immunoglobulin. Nuclear staining is of three types;* (a) *speckled* (×470), (b) *membranous* (×750), *and* (c) *diffuse* (×750). *Polygonal staining pattern at the cell periphery in* (c) *is due to presence of antibody to smooth muscle protein*

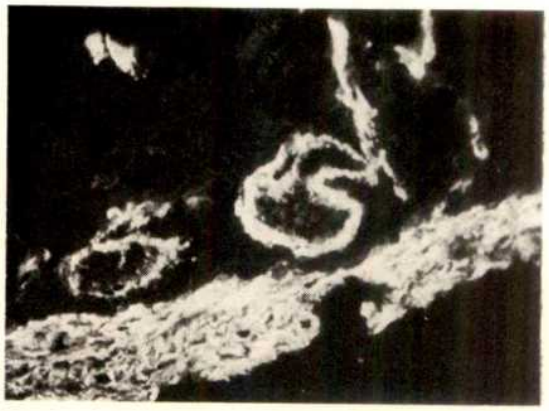

FIG. 2 *Cryostat section of rat stomach pre-incubated with patient's serum and treated with labelled antihuman IgG showing bright fluorescence in muscularis mucosae and vascular medial tunic.* ×470

body concentrations of less than 5 mg/100 ml, ++ approximated to 10 mg/100 ml, and +++ corresponded to a concentration of about 20 mg antibody/100 ml.

Results

The most striking serological finding (Table I) was the increased incidence of antinuclear antibodies in the more severely affected patients ($P < 0.001$), the pattern of immunofluorescence including diffuse, speckled, and membranous forms (Figs 1*a, b, c*). A rather less-distinct increase in incidence of antibody to smooth muscle was also observed in this group ($P < 0.05$) (Figs 1*c* and 2). Levels of immunoglobulins G, A, and M and other autoantibodies were not significantly different from those measured in control subjects. The only appreciable abnormality in the immunoelectrophoresis of tears in the patients was a reduction of secretory IgA, and this was found more frequently in the severely affected individuals (Table II).

Table II *Immunoelectrophoresis of tears in healthy individuals and in patients with practolol-induced ocular disease*

Group	*No. tested*	*Total IgA*	*Secretory IgA*	*IgG*	*Transferrin*	*Albumin*	*Lysozyme*
Healthy subjects	20	+++	++	+	+	+	+
Group A	7 (+1*)	+++	− in 6 + in 2	+	+	+	+
Group B	8	+++	+++ in 5 ± in 2 − in 1	+	+	+	+

*In one patient involvement was unilateral only: secretory IgA was absent from the tears of the affected eye but present in the contralateral eye

Discussion

The pathogenesis of the ocular and extraocular disturbances which can complicate practolol administration in certain individuals is obscure. IgG antibodies with an affinity for the intercellular region of squamous epithelium are usually, if not invariably, found. They are not obviously associated with structural damage to the cells, since they can be demonstrated in areas of healthy skin from patients with rashes involving other sites and do not seem to affect the desmosomes of corneal epithelium examined electron microscopically (Rahi and others, 1976). Moreover, although fixation of complement in the epidermis has been reported (Felix, Ive, and Dahl, 1974), we have not been able to produce convincing proof of such a reaction in ocular tissues (Rahi and others, 1976) and, since there is little to suggest an IgE-mediated response (Assem and Banks, 1973), there would seem to be scant evidence that the antibodies which are located in the epithelium have any cytotoxic effect.

The presence of antinuclear antibodies in a significant proportion of the patients we examined, particularly the more severely affected, invites comparison with certain drug-induced syndromes which resemble systemic lupus erythematosus. In such cases it has been suggested that the drug (procainamide, hydrallazine, etc.) is metabolized in a way which causes it to react with nucleoprotein so that the nucleoprotein becomes autoantigenic (Blomgren and Vaughan, 1968; Tan, 1968). So far as practolol toxicity is concerned the extent to which antinuclear antibody produces tissue damage is unknown, although there is one report (Raftery and Denman, 1973) of membranous glomerular lesions which might be construed as evidence of a harmful deposition of nucleoprotein-antinuclear antibody complex.

In spontaneous autoimmune disorders, especially those which are organ-specific, it is common to find antibodies to a variety of tissues in addition to the target organ but, apart from a marginal increase in smooth muscle antibodies in the more severely affected patients, this was not a feature of the practolol associated disease.

The absence or reduced amount of secretory IgA in the tears is almost certainly a measure of injury to the lacrimal gland, since the presence of apparently normal amounts of unconjugated IgA showed that there was no defect in antibody synthesis. This finding could be useful in assessing the degree of ocular involvement in patients at risk. Absence of the secretory component could, theoretically, reduce the capacity of IgA to combat infection in the outer eye but there is little to suggest that this was of practical importance and it is to be noted that the secretion of other antimicrobial factors, such as transferrin and lysozyme, was not noticeably impaired. Whether the parenchymal damage in the lacrimal gland is directly produced by the drug or its metabolites or if it is related to immunological activity is not known. Evidence that practolol may accumulate innocuously in lacrimal tissue of laboratory animals is difficult to evaluate since the ocular side-effects of the drug appear to be confined to man. Possibly the susceptibility to ocular disturbance is related to peculiarities in metabolism of the drug in a few individuals, so altering both nucleoprotein and other tissue antigens and rendering them autoantigenic and, at the same time, specifically damaging lacrimal gland epithelium.

Summary

Serological studies in 22 patients presenting with ocular disease attributable to dosage with the β-blocking agent practolol revealed a raised incidence of antinuclear antibodies. There was also a marginal increase in the incidence of antibodies to smooth muscle in the more severely affected individuals but the incidence of other autoantibodies and levels of IgG, IgA, and IgM were within normal limits. Semi-quantitative analysis of tears from 14 of the patients showed absence or near absence in the more severely affected patients of secretory IgA, which is indicative of damage to the lacrimal gland. Other immunological parameters in the tears were normal.

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Rapid pneumatic and Mackay-Marg applanation tonometry to evaluate the postural effect on intraocular pressure

M. R. JAIN AND V. J. MARMION
From Bristol Eye Hospital, Bristol

Glaucoma is usually considered to be adequately controlled when Goldmann applanation readings are below 22 mmHg. It is, however, now known that the intraocular pressure increases to a varying degree when the patient changes his posture from sitting to a recumbent position (Galin, McIvor, and Magruder, 1963; Roberts and Rogers, 1964; Hetland-Eriksen, 1966a; Inglima, 1966; Tarkkanen and Leikola, 1967; Langham and McCarthy, 1968; Anderson and Grant, 1973). Hetland-Eriksen (1966a, b) stated that the increase in intraocular pressure when in a recumbent position is in some way directly proportional to the initial intraocular pressure; this complicates our dependence on Goldmann tonometry as that procedure is performed routinely only in the sitting position.

The present study, as well as making a clinical evaluation of the Mackay-Marg tonometer and the pneumatonograph, assesses the relationship of various postures to intraocular pressure in normal and glaucomatous eyes. The study was conducted using two of the more modern rapid applanation tonometers: the pneumatonograph (PTG)* and the Mackay-Marg electric tonometer† as both are easily portable and continuously monitor the pressure on graph paper, and in addition, they can be used in any posture with equal ease and precision. Neither do they require the magnification or illumination of a slit-lamp nor the use of fluorescein, as is essential in Goldmann tonometry. The pneumatonograph (Jain and Marmion, 1976) and the Mackay-Marg (Kaufman, Wind, and Waltman, 1970) can be used to record exact pressures in cases of ectatic corneas or postkeratoplasty (Irvine and Kaufman, 1969) as it is not imperative to apply the tip of the probe to the centre of the cornea in either procedure.

The correlation of the PTG (Jain and Marmion, 1976) and the Mackay-Marg (Tierney and Rubin, 1966) with the Goldmann has been shown to be significant, although the mean pressures recorded by the PTG and the Mackay-Marg are reported to be about 1 and 2 mm higher than those using the Goldmann.

The main difference between the two instruments is that the pneumatonograph is a combination of a pneumatic and an electronic system, whereas the Mackay-Marg is purely electronic and, when applanated, its recording system is driven by the slightest movement of the fuzed quartz plunger rod. The pneumatonograph has the advantage that the applanation is confirmed by a continuous whistle and the pressure can be read instantaneously from the digital display as well as from recordings on the chart. Applanation is simpler with the Mackay-Marg but its accuracy cannot be confirmed and hence it is essential to make 4 to 5 applanations each time to obtain a correct recording. The Mackay-Marg tonometer requires calibration daily before use, whereas the PTG need be calibrated only once a week. The Mackay-Marg is quicker in the sense that single applanation requires only about a second whereas the PTG requires 2 to 5 seconds.

Precise study of amplitude of ocular pulse with the PTG is a distinct advantage in the diagnosis of carotid occlusion, since the amplitude of ocular pulse is significantly affected even in cases with 20 per cent carotid obstruction (Best and Rogers, 1974).

Material and methods

The cases studied comprised three groups. Group 1 consisted of 20 normal young volunteers (40 eyes) with an age range of between 15 and 29 years. The postural study in this group was conducted only by the pneumatonograph.

Group 2 consisted of patients without glaucoma, routinely attending the outpatient clinic and who corresponded in age with the glaucomatous subjects. Patients included in this group were completely normal, cataractous, aphakics, or had defective vision or, in some cases, had some retinal disease such as diabetic retinitis, retinitis pigmentosa, etc.

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*Alcon Applanation Pneumatonograph TM, Alcon Universal Ltd, Fortworth, USA

†Berkely Model 255 Mackay-Marg Electronic Tonometer with Model Probe 200

Address for reprints: V. J. Marmion, Consultant Ophthalmic Surgeon, Bristol Eye Hospital, Bristol

Group 3 were all patients with open-angle glaucoma and were selected as follows:

Those with previously undiagnosed glaucoma with intraocular pressures exceeding 22 mmHg.

Those receiving treatment but with intraocular pressures exceeding 20 mmHg.

Group 3 also included adequately controlled glaucomatous patients who were advised to stop treatment for at least 24 hours before the study was conducted. Patients in this group were selected according to their initial sitting pressure readings using the pneumatonograph. The number of patients included in Group 2 was 76 (151 eyes) and in Group 3 54 (108 eyes) with an age range of between 30 and 85 years.

The pneumatonograph and the Mackay-Marg instruments were connected to the mains, adjusted, and calibrated as required. The Mackay-Marg tonometer used in this study required calibration to 9·5. The PTG sensor tip has to be sterilized in 70 per cent isopropyl alcohol and a new autoclaved thin rubber tonocover was used for each new patient for the Mackay-Marg probe. The sequence of examination in this study was as follows.

The patient was comfortably seated erect on an examination couch and the eyes were anaesthetized with drops of 0·4 per cent benoxinate hydrochloride. The patient was asked to fix some object and avoid squeezing while he held his gaze. The tip of the Mackay-Marg probe was applanated to the apical zone of the cornea for about half a second. Four to five applanations were repeated in each eye. While applanating, care was taken that the centre of the probe was the first thing to make contact with the cornea and the withdrawal was abrupt. Soon after, with the patient in the same position, the tip of the PTG sensor probe was applanated to the apical zone of the cornea for about two to five seconds. A correct applanation was confirmed by a continuous whistle from the machine and the intraocular pressure was displayed as well as being recorded on the chart.

Thereafter, the patient was asked to lie face upwards on the same couch and, after two minutes, the pressure was recorded by both the Mackay-Marg and the PTG. The patient continued to lie in the same position and the pressure was re-recorded after three minutes using the same instruments. Then a pillow with an effective thickness of 12·7 cm was placed underneath the patient's head and pressure was recorded after two minutes. Having done that, the patient was made to sit erect as originally and the pressure was recorded at two- and five-minute intervals. This way, with both tonometers, six separate pressure readings were obtained in various postures for each patient in Groups 2 and 3.

To make the study more valid the following precautions were taken:

1. All measurements were performed by the same examiner.
2. The Mackay-Marg tonometer was calibrated daily and the PTG once in seven days.
3. All examinations were conducted on the same examination couch and hence the patient was not required to walk even a single step.
4. Patients were requested to keep their eyes gently closed during intervals to avoid any evaporation from anaesthetized cornea.

Results

AGE AND SEX DISTRIBUTION (Fig. 1)

In Group 1, the average age was 20·75 years and all the volunteers were women. In Groups 2 and 3, the ages ranged between 30 and 85 years with an average of 61·72 years, but in most cases (80·77 per cent) the ages ranged between 50 and 79 years with women predominating in almost all age groups giving an overall ratio of 13 : 9.

PNEUMATONOGRAPH READINGS COMPARED WITH MACKAY-MARG

Fig. 2 is the complete scattergram for Groups 2 and 3 (259 eyes). The Mackay-Marg readings are plotted on the ordinate and the pneumatonograph on the abscissa. The correlation coefficient (R) is

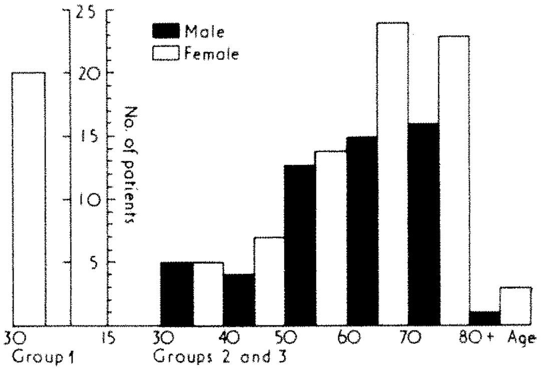

FIG. 1 *Ages and sexes in Groups* 1, 2, *and* 3 (150 *cases*)

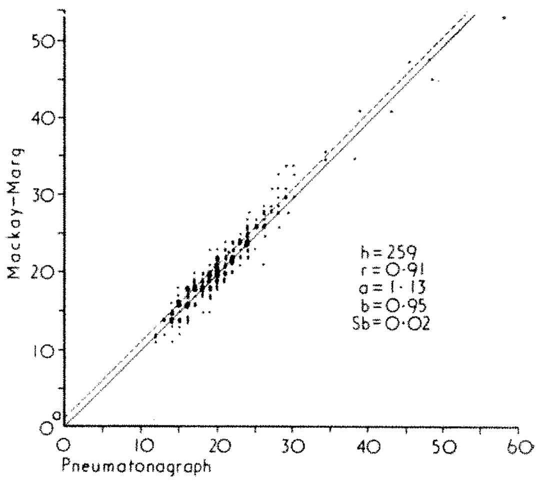

FIG. 2 *Scattergram showing pneumatonograph and Mackay-Marg intraocular pressure readings for* 259 *eyes (Groups* 2 *and* 3*) in initial sitting posture*

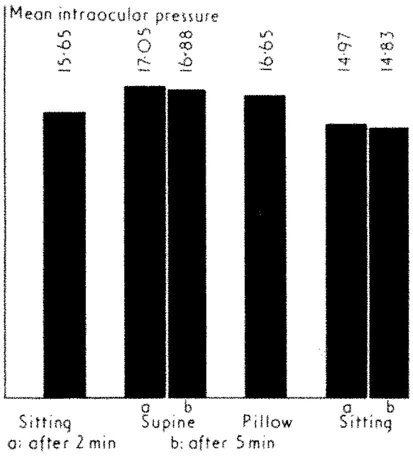

FIG. 3 *Mean postural pressures in Group* 1 *volunteers* (40 *eyes) as recorded by pneumatonograph*

0·91. The calculated slope of the line is 0·95 *(b)* and the standard error of the slope is 0·02. The intercept *(a)* is 1·13 and is interpreted to mean that the average Mackay-Marg reading is about 1 mmHg higher than the pneumatonograph reading.

POSTURAL CHANGE IN PRESSURE

Group 1 (Fig. 3). The mean initial intraocular pressure as recorded by the PTG was 15·65 ±0·25 mmHg. There was an average increase in pressure of 1·4 mmHg within two minutes after lying supine (supine-a), then a slight decrease in supine (b) and 'pillow' positions, but the decrease was significant when the patient was again sitting. The mean intraocular pressure recorded in the end (sitting-b) was 0·82 mmHg lower compared with the initial sitting intraocular pressure.

Groups 2 *and* 3. The results of the mean, standard error of the mean, and standard deviations of intraocular pressure recordings in various positions using the PTG and the Mackay-Marg tonometer for Groups 2 and 3, combined and separately, are shown in Fig. 4. The mean pressure recordings by Mackay-Marg were uniformly higher by approximately 1 mmHg in all positions. Fig. 4 and Table I also show that there was a statistically significant increase in intraocular pressure when the patient changed from sitting to lying. The range of rise in pressure in non-glaucomatous subjects was –2 to –8 mmHg and in glaucomatous eyes it ranged between 0 and 10 mmHg. The mean rise in pressure using the PTG was 2·71, 4·04, and 3·28 mmHg in Groups 2, 3, and 2 plus 3, respectively. Using the Mackay-Marg it was 2·51, 3·72, and 2·79 mmHg in the same order. After this initial rise, there was a slight fall in pressure in the supine posture and a greater fall when the pillow was placed under the head, but the fall was significant (mean fall ranging between 1·15 and 1·95 mmHg) compared with the

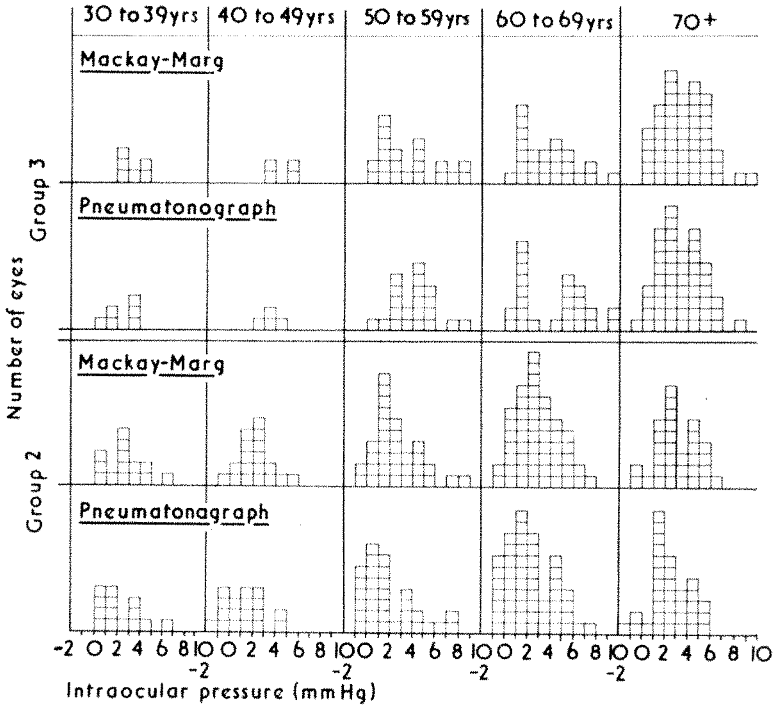

FIG. 4 *Results of mean, standard error of mean, and standard deviations of pressure in Groups* 2, 3, *and* 2 *plus* 3 *in various postures as recorded by PTG and Mackay-Marg tonometer*

Table I *Mean and range of variation in intraocular pressure in different postures in group 2 and group 3 separately and combined as recorded by pneumatonograph and Mackay-Marg tonometer*

Groups		*Pneumatonograph*					*Mackay-Marg tonometer*				
		1	2	3	4	5	1	2	3	4	5
2	Mean (mmHg)	2·71	0·26	0·44	0·30	1·15	2·51	0·30	0·32	0·41	1·33
(151 eyes)	Range (mmHg)	–2 to 8	–2 to 3	–1 to 3	–2 to 3	0 to 3	–1 to 8	–2 to 4	–1 to 4	–3 to 3	0 to 4
3	Mean (mmHg)	4·04	0·74	0·64	0·85	1·56	3·72	0·96	0·86	0·93	1·95
(108 eyes)	Range (mmHg)	0 to 10	–3 to 4	–2 to 3	–2 to 4	0 to 5	0 to 10	–2 to 4	–2 to 4	–3 to 5	0 to 5
2 and 3	Mean (mmHg)	3·28	0·46	0·52	0·57	1·32	2·79	0·55	0·57	0·54	1·81
(259 eyes)	Range (mmHg)	–2 to 10	–3 to 4	–2 to 3	–2 to 4	0 to 5	–1 to 10	–2 to 4	–2 to 4	–3 to 5	0 to 5

1 = Supine (2 min) minus sitting (initial); 2 = Supine (2 min) minus supine (5 min); 3 = Supine (5 min) minus pillow under head; 4 = Sitting (2 min) minus sitting (5 min); 5 = Sitting (initial) minus sitting (5 min)

initial pressure when the patient was again sitting (Table I). The variation in pressure was greater in glaucomatous than in non-glaucomatous subjects. The classical clinical PTG pressure recordings in various postures in two typical cases is shown in Figs 5 and 6.

The results shown in Table II explore the possibility of any relationship in age with the postural rise in pressure. There were few patients in the age groups 30 to 39 and 80+ and if they are excluded there would appear to be a direct relationship between postural rise in pressure and age in the age group 50 to 79 years in Group 2, as shown by recordings of both the PTG and the Mackay-Marg (Table II). Fig. 7, which shows the frequency distribution of postural pressure rise in Groups 2 and 3 at various ages confirms this observation. Comparative postural rise to a higher degree is evident in older age groups, particularly in glaucomatous patients; 16·67 per cent in Group 2 and 5·34 per cent eyes in Group 3 showed no change in pressure as recorded by the PTG, and 14 per cent of Group 2 even showed a fall in pressure of 1 to 2 mmHg by PTG. In none of the

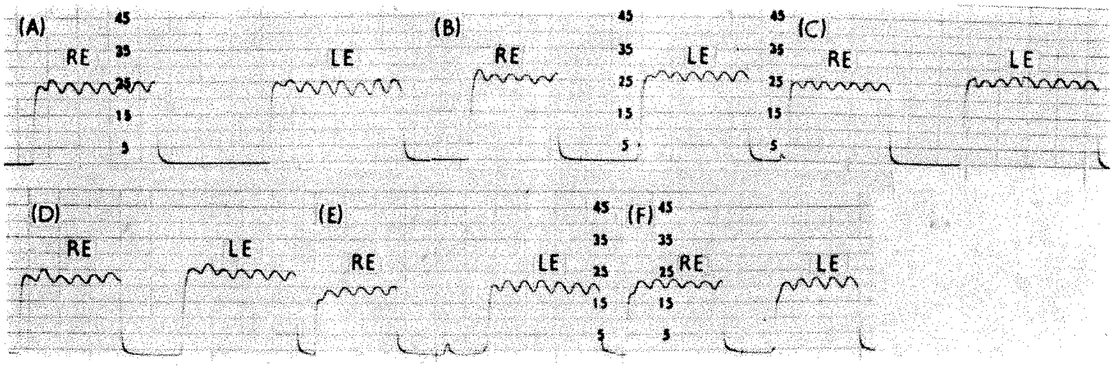

FIG. 5 *Shows clinical PTG pressure recordings of both eyes in various postures*—(a) *sitting*, (b) *supine 2 min*, (c) *supine 5 min*, (d) *pillow under head*, (e) *sitting 2 min*, (f) *sitting 5 min*

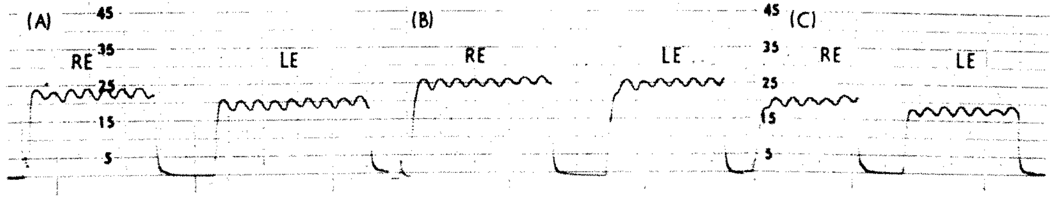

FIG. 6 *Clinical PTG pressure recordings in three postures*—(a) *sitting*, (b) *supine*, (c) *sitting*

Table II *Mean rise in intraocular pressure in various age groups from sitting to supine (2 minutes) posture in group 2 and 3 as recorded by PTG and Mackay-Marg tonometer*

Age groups	*No. of eyes*	*Group 2*	*Group 3*	*Mean postural change (sitting to supine—2 min)*			
				Pneumatonograph		*Mackay-Marg*	
				Group 2	*Group 3*	*Group 2*	*Group 3*
30 to 39	20	14	6	2·78	2·83	2·54	2·92
40 to 49	22	18	4	1·87	4·00	2·00	3·75
50 to 59	54	33	21	2·73	4·20	2·32	4·24
60 to 69	77	52	25	2·79	4·80	2·45	4·67
70 to 79	78	32	46	3·09	4·10	2·85	4·24
80+	8	2	6	3·00	3·17	2·95	3·21
Total	259	151	108	16·26	24·54	15·31	23·03
			Mean	2·71	4·04	2·51	3·72

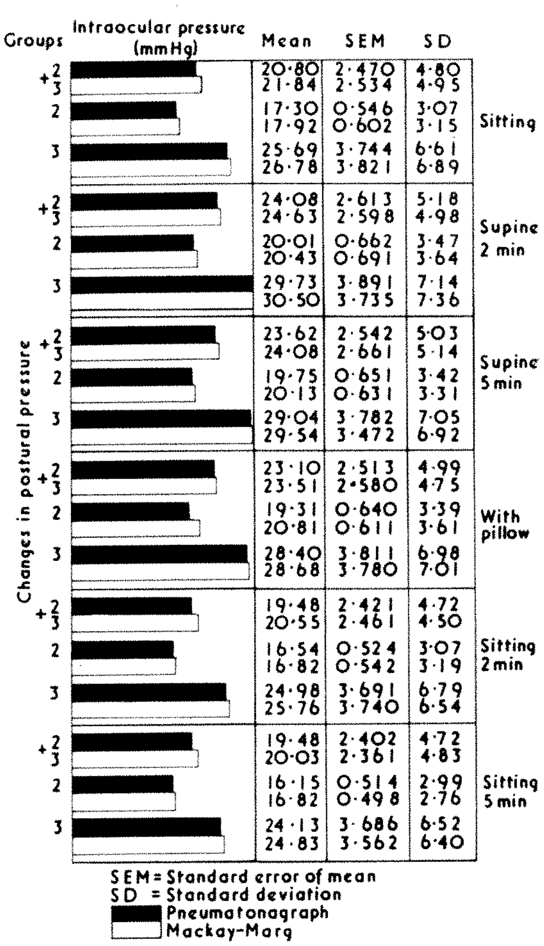

FIG. 7 *Frequency distribution histogram of change in pressure from sitting to supine (two minutes) in relation to age groups in Groups 2 and 3 by PTG and Mackay-Marg tonometer*

glaucomatous patients was there any fall in pressure when in the supine position.

On the whole, the increase most frequently observed in Group 2 was of 1 to 2 mmHg in 40 per cent by the PTG and in 46 per cent by the Mackay-Marg, whereas in Group 3 it was 2 to 3 mmHg. In Group 2, an increase in pressure of 5 mmHg or more was observed in 12·67 per cent using the PTG and 9·34 per cent using the Mackay-Marg, whereas in Group 3 it was 25 and 27·78 per cent, suggesting higher frequency of high postural change in glaucomatous patients compared with non-glaucomatous subjects.

Discussion

The first indentation tonometer was introduced by the Utrecht School, but the most reliable instrument during the first half of the twentieth century was undoubtedly the Schiötz (1909). Weighted applanation tonometry was first conceived by Maklakoff in 1885 and a resurgence of interest in applanation tonometry in the more scientific form (Goldmann, 1957) greatly improved the accuracy of this form of measurement. Both indentation and Maklakoff applanation tonometry are carried out when the patient is lying down. Goldmann applanation tonometry, on the other hand, is carried out when the patient is erect. For this, among other reasons, it is difficult to compare the two methods. An investigation of this difference has led to the discovery that postural pressure changes occur, but that both the Mackay-Marg tonometer and the pneumatonograph operate independently of posture.

Tierney and Rubin (1966) showed that the Mackay-Marg tonometer corresponds with the Goldmann applanation method to within 2 mmHg. The work of Quigley and Langham (1975) and Jain and Marmion (1976) has shown that the PTG and

Table III *Comparative figures of postural increase in intraocular pressure as observed by various workers*

	No. of eyes	*Mean IOP while sitting (mmHg)*	*Mean increase in pressure (mmHg)*	*Instrument used*	
				Sitting	*Recumbent*
Armaly and Salamoun (1963)	76	14·73	2·63	Goldmann	Goldmann (lying on side)
Galin and others (1963)	40	15·63	3·04	Goldmann	Goldmann (lying on side)
Robert and Rogers (1964)	151	18·80	2·20	Goldmann	Goldmann (supine)
Hetland-Eriksen (1966a)	76	32·57	4·74	Goldmann	Goldmann (lying on side)
Tarkkanen and Leikola (1967)	74	15·0	1·40	Mackay-Marg	Mackay-Marg (supine)
Krieglestein and Langham (1975)	90	14·0	2·50	PTG	PTG (supine)
	32	17·0	4·30	PTG	PTG (supine)
	20	28·9	5·00	PTG	PTG (supine)
Jain and Marmion (1976)					
Group 1	40	15·65	1·40	PTG	PTG (supine)
Group 2	151	17·30	2·71	PTG	PTG (supine)
		17·92	2·51	Mackay-Marg	Mackay-Marg (supine)
Group 3	108	25·69	4·04	PTG	PTG (supine)
		26·78	3·72	Mackay-Marg	Mackay-Marg (supine)
Groups 2 and 3	259	20·80	3·28	PTG	PTG (supine)
		21·84	2·79	Mackay-Marg	Mackay-Marg (supine)

Goldmann readings correspond in normal eyes to within less than 1 mmHg. The current study on intraocular pressure on 259 eyes using the PTG and the Mackay-Marg indirectly confirmed these observations and showed that the mean reading using the Mackay-Marg was higher by 1·13 mmHg than that of the PTG. Consistency of readings in each instrument served as a cross check on the postural change in intraocular pressure.

There is a significant increase in intraocular pressure when a normal subject changes from sitting to lying down. Although Fig. 4 and Table I indicate that there is some degree of a decrease in pressure within five minutes of assuming the recumbent posture, a sample of 15 patients (30 eyes) after the initial five-minute period showed a degree of consistency in the recordings which suggests that any fall occurring after that time would be slight. A reduction in the degree of increase in intraocular pressure is mitigated by adoption of a semi-recumbent position (one pillow) which raises the head to about fifteen degrees, and a return to the original or less than the original pressure occurs on resuming the erect posture.

The rise in intraocular pressure is dependent partly on the initial intraocular pressure, but this increase is significantly higher in the 50 to 79 year age group. This takes into account the rectification required for disparity in numbers, the proportion of women to men, and the initial difference in intraocular pressures. The results for young people correlate well with those of Tarkkanen and Leikola (1967), although the average age was higher in their report and the mean intraocular pressure slightly lower (Table III). In the older age group comparable to the distribution in chronic simple glaucoma, the results obtained confirm those published by Armaly and Salamoun (1963), Galin and others (1963), and Robert and Rogers (1964). The mean postural pressure changes were higher than in the Group 2 reported here, particularly in the recumbent position, partly because the patients were examined lying on their sides. The results of Quigley and Langham (1975) are uniformly higher for which there is at present no explanation.

The principal postural changes in circulatory dynamics are related to changes in the blood volume which decreases in the erect posture after about 30 minutes as a result of hydrostatic capillary changes. There is a fall in blood pressure in recumbency associated with increased minute volume which occurs rapidly, usually within 30 seconds. The rapidity with which the intraocular pressure increases in the recumbent position would indicate that this is a reflex phenomenon governed by a baroreceptor type mechanism, and the fine adjustment that can occur in time and on adjustment of posture supports this hypothesis. Hydrostatic changes as mediated through venous pressure, capillary perfusion, and blood volume movements, would take longer to produce an effect by change in posture. Age would also tend to accentuate this change and if the baroreceptor mechanism were the basis for it, it would be expected that this would increase with age.

The mean postural change in glaucomatous patients is significantly higher than in the non-glaucomatous group. This is basically in agreement with the work of Hetland-Eriksen (1966a) and Krieglestein and Langham (1975), but it was neither universal nor uniform (Fig. 7); 8 per cent of glaucomatous eyes had no change in intraocular pressure, 24 per cent had an increase which was within the bounds noted on a normal gaussian curve, and an increase in intraocular pressure of more than 5 mmHg was observed approximately three times more frequently in glaucomatous than in non-glaucomatous eyes. The maximum rise recorded by us was 10 mmHg in glaucomatous eyes and 8 mmHg in non-glaucomatous eyes. The glaucomatous eyes take longer to adjust after the rise, as shown by the divergence of results in the semi-recumbent to erect posture. This reflects the inability of the glaucomatous eye to compensate for change in pressure and offers a simple testing method for potential glaucomatous change in aqueous humour dynamics. If the postural changes in pressures are going to be used as a diagnostic procedure in glaucoma, it is important to take into account that aspect of the orientation of the pressure, particularly if the postural rise has not been very remarkable.

Four further clinical aspects of the postural rise merit consideration. First, the role posture can play in the production of change at the optic disc in cases of glaucoma and so-called low-tension glaucoma where the increased intraocular pressure when lying down is associated with a fall in blood pressure, although this may be partly mitigated by a slightly increased blood volume. Secondly, medical treatment cannot be regarded as being successful unless the highest intraocular pressure can be contained within normal limits for a particular eye. This is so for stressful conditions, diurnal rises, and also postural changes in pressure. Thirdly, the effect of surgery on the postural rise is important because of the initial reverse effect during the actual operative procedure and, also in the event of surgery proving better in controlling the glaucomatous rise in recumbency, it would be an indication for opting for this course of treatment. Finally, the postural pressure rise should be of consideration in all intraocular operations and may possibly account for some of the vitreous problems such as vitreous upthrust in cataract surgery.

The mechanism of the glaucomatous postural change should be examined further in conjunction with phasic variation, plasma cortisone fluctuation, and other hydrostatic mechanisms. Such investigations could possibly give some indication to the basic mechanism of the response and the variation that occurs.

Summary

A postural study was conducted in three separate groups of subjects. The first group comprised 20 women volunteers with an average age of 20·75 years. In this group, the study was conducted by the pneumatonograph only. Mean pressure recorded was 15·65 ±0·25 mmHg and there was an average rise of 1·4 mmHg in supine posture.

Groups 2 and 3 comprised 151 non-glaucomatous and 108 glaucomatous eyes respectively in the age range of 30 to 85 years. In these two groups, the study was conducted using the PTG and the Mackay-Marg tonometer. Clinical evaluation of the Mackay-Marg with the PTG gave significant correlation, with mean Mackay-Marg readings being 1·13 mmHg higher.

The intraocular pressure when changing from seated to the supine position increased on average by 2·71 and 4·04 mmHg, respectively in Groups 2 and 3 and by 2·51 and 3·72 mmHg by Mackay-Marg, suggesting a higher change in glaucomatous subjects. Pressure on resumption of sitting was found to be lower than the initial pressure. Postural change also showed some direct relationship with age in non-glaucomatous subjects.

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Chronic retinal vein occlusion in glaucoma

R. A. HITCHINGS AND G. L. SPAETH
From Moorfields Eye Hospital, London, and Wills Eye Hospital

An association between acute central retinal vein occlusion and chronic simple glaucoma has been recognized for many years (Moore, 1922; Braendstrupp, 1950; Becker and Post, 1951; Bertelson, 1961; Raitta, 1965). The incidence of glaucoma in acute central retinal vein occlusion is reported to range from 9 to 43 per cent (Braendstrupp, 1950; Bertelson, 1961). In most instances, the patients were not known to have glaucoma before development of the occlusion (Sugar, 1942; Braendstrupp, 1950; Vannas and Tarkkanen, 1960); in cases in whom glaucoma was present, it was not far advanced (Bertelson, 1961; Wise, Dollery, and Henkind, 1971a).

The relationship of retinal vein occlusion with cases of long-standing chronic simple glaucoma is less well understood. Bertelson (1961) did not find a single case of central retinal vein occlusion on reviewing 296 eyes with 'mainly chronic' glaucoma (Bertelson, 1961). Dobree (1957), in a survey of 200 glaucomatous eyes, found eight eyes with abnormal venous channels on the optic disc that might have indicated an earlier central retinal vein occlusion. Wise and others (1971b) felt that the 'usual type of vein obstruction due to glaucoma is occlusion of the central retinal vein late in any kind of chronic glaucoma. The obstruction develops insidiously in cases with moderate to marked cupping of the disc'. Kohner and Shilling (1976) when discussing branch retinal vein occlusions felt that a hemisphere vein occlusion, where the occlusion occurred 'on the optic disc at the edge of the optic cup' was a type of vein occlusion unquestionably associated with chronic glaucoma.

The diversity of opinion prompted this investigation into the relationship of retinal vein occlusion with chronic glaucoma.

It is the purpose of this paper to describe the clinical features of central and hemisphere retinal vein occlusion in glaucoma. The incidence of these types of retinal vein occlusion in patients attending a glaucoma clinic will be given. Finally, the effect that those retinal vein occlusions may have on the prognosis for the glaucoma will be discussed.

Address for reprints: R. A. Hitchings, FRCS, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

Material and methods

Patients attending the Glaucoma Service at Wills Eye Hospital between October 1973 and April 1975 were examined for evidence of earlier central or hemisphere retinal vein occlusion. Occlusion of the central retinal vein was considered to have occurred if retino-ciliary collateral channels on the optic disc or vein loops on the disc surface, suggesting collaterals within the disc, were discovered (Wise and others, 1971c). A hemisphere vein occlusion was considered to have occurred if veno-venous anastomoses nasal and temporal to the optic disc along a horizontal meridian were present.

Patients diagnosed as having suffered an earlier retinal vein occlusion were subjected to a full ophthalmic examination. This included applanation tonometry, gonioscopy, fundoscopy, and an examination of the visual field with a Goldmann perimeter using two, and usually three, different sized test objects. In addition, Goldmann and Hruby lens examination of the posterior pole, ophthalmodynamometry corrected for intraocular pressure, stereoscopic disc photography, and fluorescein angiography were carried out whenever possible. (In several patients these examinations were precluded by permanently miosed pupils, and/or lens opacities.) Particular note was made of the presence or absence of spontaneous pulsation of the retinal veins on the optic disc, and the existence of retinal haemorrhages and exudates.

Results

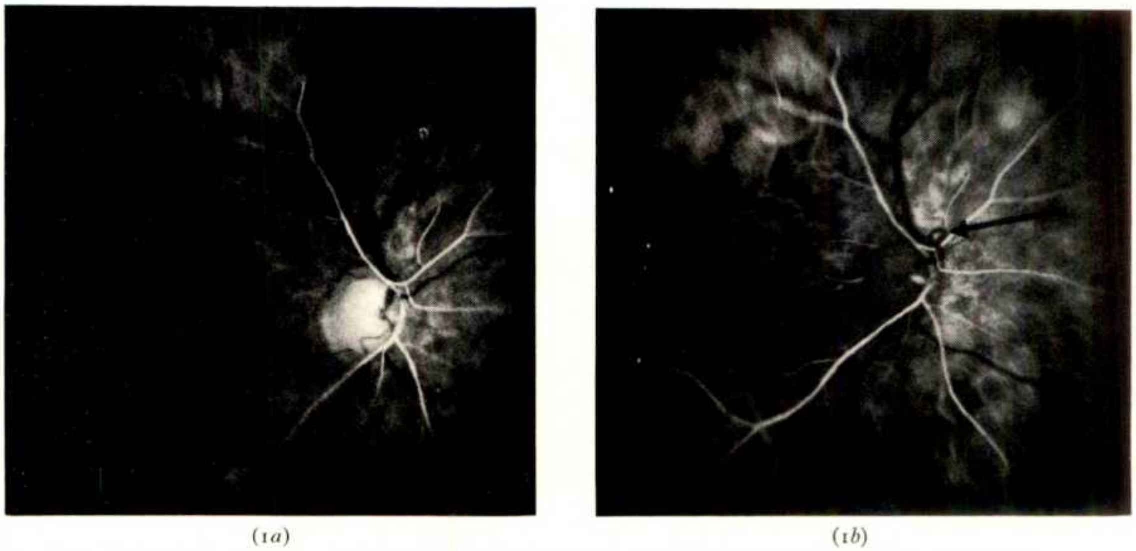
Eighteen patients—10 White and eight Black—(26 eyes) had evidence of earlier central or hemisphere retinal vein occlusion. This number comprised 2 per cent of patients attending the Glaucoma Service during the study period. These patients could be divided into two groups:

Group I: End stage glaucoma:

a. With venous loops and/or collateral vessels identifiable on the optic disc: eight patients, 14 eyes
b. With retinal veno-venous anastomoses: four patients, four eyes

Group II: Early-moderate glaucoma:

With venous loops and/or collateral vessels identifiable on the optic disc: six patients, eight eyes



(1*a*) (1*b*)

FIG. 1 a and b *(Patient 6) Demonstrates development of a venous loop (arrowed) within a 22-month period*

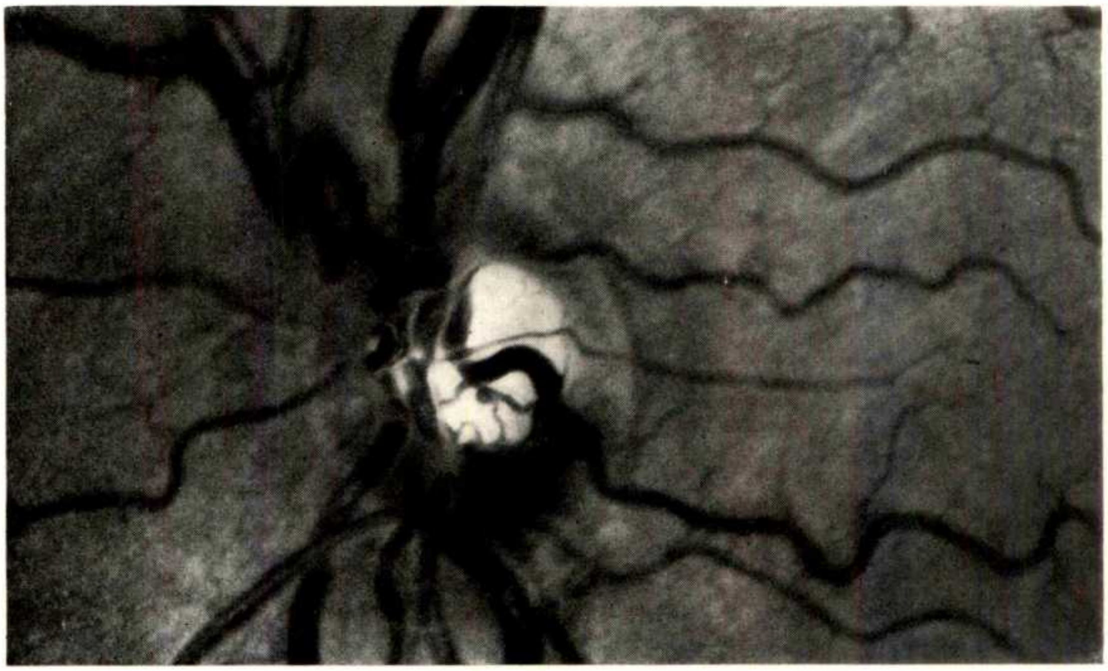


FIG. 2 *(Patient 16) Multiple venous loops in patient with glaucomatous cupping and no loss of visual field*

End stage glaucoma refers to eyes with a central field of 10° or less, or a residual temporal island. Early to moderate glaucoma refers to eyes with raised intraocular pressures and definitely cupped optic discs with visual field loss ranging from minimal or no field-loss to a loss of approximately one-half of the visual field.

The clinical features of these patients are shown in the Table. The development of venous loops within a 22-month period is shown in Figs 1*a*, *b*, Patient 6. Marked venous loops in a patient with cupping and no field loss are shown in Fig. 2, Patient 16. Multiple veno-venous anastomoses are shown in Fig. 3, Patient 10.

Table *Clinical data of patients with chronic retinal vein occlusion*

Patient no.	*Group no.*	*Date of examination*	*Age (years)*	*Sex*	*Race*	*Visual acuity*		*Visual field*		*Intrao pressu*
						Right	*Left*	*Right*	*Left*	*Right*
1	Ia	30.03.73	40	Female	Black	6/9	NPL	5° Central island	Nil	44
		13.08.74	41			6/9	NPL	Unchanged	Unchanged	20
2	Ia	29.08.74	73	Male	White	CF	CF	Temporal island	Temporal island	60
3	Ia	15.01.74	68	Female	White	6/60	HM	5° Central field	5° Central field	58
4	Ia	20.11.73	40	Male	Black	6/60	HM	5° Central island	3° Central island	38
		23.01.75	41			6/60	HM	Unchanged	Unchanged	14
5	Ia	26.08.70	72	Male	Black	6/12	HM	5° Central island	3° Central island	30
		01.07.74	76			6/60	NPL	3° Central island	Nil	22
6	Ia	26.03.71	53	Female	White	6/15	6/9	Lower arcuate	Full	30
		18.03.73	55			HM	6/6	Temporal island	Full	50
		28.01.74	56			HM	6/6	Temporal island	Full	18
7	Ia	25.09.74	60	Female	Black	HM	6/5	Temporal island	Full	50
8	Ib	09.09.74	77	Female	White	6/9	6/9	Superior altitudinal hemianopia	Superior altitudinal hemianopia	32
9	Ib	19.02.72	43	Male	Black	NPL	6/9	Nil	Lower arcuate	35
		20.02.75	46			NPL	6/24	Unchanged	Unchanged	17
10	Ib	27.01.75	46	Male	Black	NPL	6/15	Nil	5° Central island	48
11	Ib	15.01.75	47	Female	Black	6/60	NPL	5° Central island	Nil	13
12‡	Ic	04.06.75	55	Female	White	6/12	6/60	5° Central island	5° Central island	50
13	II	03.02.71	37	Female	White	6/12	6/15	Apparently full	Apparently full	57
		17.04.74	50			6/12	6/15	Unchanged	Unchanged	14
		17.02.75	51			6/12	6/15	Unchanged	Unchanged	12
14	II	08.01.73	45	Female	Black	6/9	6/60	Lower sector defect	Lower sector defect	33
		23.03.74	46			6/9	6/60	Unchanged	Unchanged	18
15	II	11.03.74	24	Male	White	6/12	6/15	Lower sector defect	Lower sector defect	57
		12.06.74	25			6/12	6/15	Unchanged	Unchanged	15
16	II	02.03.75	22	Male	White	6/9 +	6/9 +	Full	Full	21
17	II	30.09.74	50	Male	White	6/9	6/9	Full	Full	20
18	II	08.02.71	33	Female	White	NPL	6/12	Nil	Lower sector defect	38
		29.06.73	35			NPL	6/9	Nil	Unchanged	34
		24.01.75	37			NPL	6/9	Nil	Unchanged	24

*ODM = Ophthalmodynamometry
‡Maculopathy right and left. Venous statis reinopathy right and left

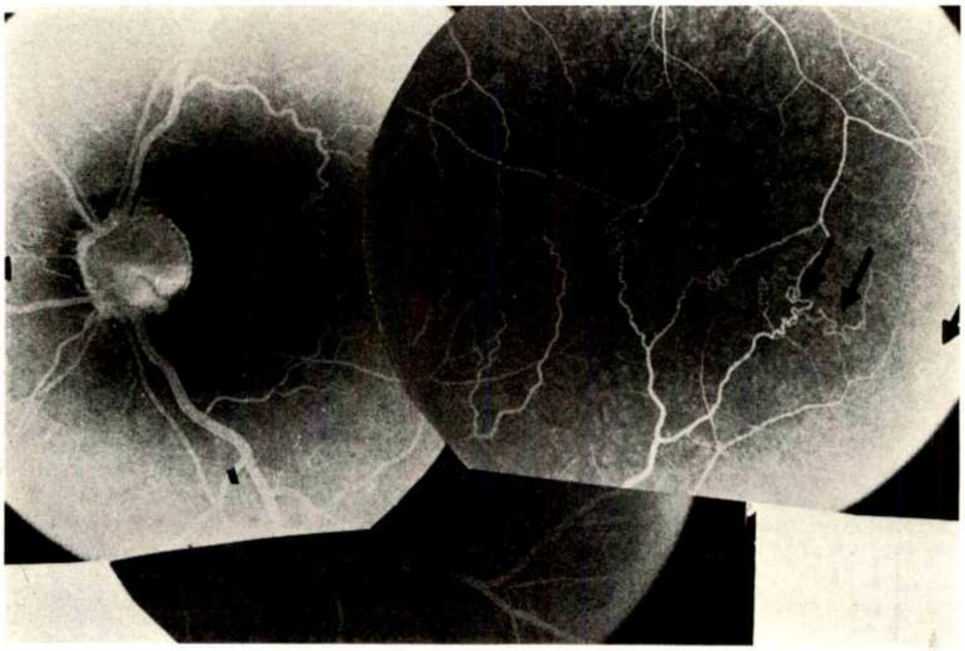


FIG. 3 *(Patient 10) Multiple veno-venous anastomoses (arrowed) in patient with hemisphere vein occlusion*

tical cup/disc o		*ODM**		*Spontaneous venous pulsation (SVP)†*		*Systemic blood pressure*	*Venous loops (L) or collaterals (C) on optic disc*		*Retinal vein anastomoses temporal to macula*	
ht	*Left*	*Right*	*Left*	*Right*	*Left*		*Right*	*Left*	*Right*	*Left*
	1·0	—	—	—	—	—	No	L	—	—
	1·0	—	—	Absent	Absent	—	No	L	—	—
	0·9	—	—	Absent	Absent	—	L, C	L, C	No	No
	0·8	—	—	Absent	Absent	140/90	L	L	No	No
	0·9	—	—	—	—	—	—	—	—	—
	0·9	75/43	64/42	Absent	Absent	116/82	L, C	L, C	No	No
	1·0	—	—	—	—	—	L	L, C	No	No
	1·0	—	—	Absent	Absent	140/86	L	L, C	No	No
	0·2	—	—	—	—	—	—	—	—	—
	0·2	—	—	—	—	—	L	No	—	—
	0·2	—	—	Absent	Present	—	L	No	No	No
	0·4	—	—	Absent	Present	—	L, C	No	No	No
	0·9	—	—	Absent	Present	—	L	L	No	Yes
	0·9	—	—	—	—	—	No	No	Yes	—
	0·9	67/35	64/38	Absent	Absent	140/94	No	No	Yes	No
	0·9	—	—	Present	Absent	122/80	No	No	No	Yes
	0·9	—	—	Present	Absent	—	No	No	No	Yes
	0·9	60/17	70/45	Absent	Absent	—	L, C	L, C	No	No
	0·8	—	—	—	—	—	—	—	—	—
	0·8	—	—	—	—	—	L	L	—	—
	0·8	55/13	60/17	Absent	Absent	120/65	L	L	No	No
	0·9	—	—	—	—	136/68	No	L	—	—
	0·9	57/35	57/35	Absent	Absent	128/76	No	L	No	No
	0·8	—	—	—	—	118/74	L	L	—	—
	0·8	60/47	60/49	Absent	Absent	132/80	L	L	No	No
	0·7	62/32	64/35	Present	Absent	124/80	No	L	No	No
	0·4	40/22	50/22	Present	Absent	122/80	No	L, C	No	No
	0·3	—	—	—	—	—	No	L	—	—
	0·8	—	—	—	—	106/62	No	L	No	—
	0·8	—	37/22	—	Absent	106/54	No	L	—	No

P referred to as absent only when elicited at, or just below ,diastolic arterial pressure; and present only when visible at the current intraocular
essure or with gentle digital pressure

Fourteen patients (22 eyes) had evidence of an earlier central retinal vein occlusion, six eyes had readily recognizable retino-ciliary collateral veins at the optic disc, the remainder had venous loops suggesting retino-ciliary collateral vessels within the optic nerve. None of these patients had a history of sudden loss of visual acuity and none had arterial attenuation or sheathing. One patient (two eyes) had (peripheral) retinal haemorrhages; these occurred in the only patient with a maculopathy. No patient had cotton-wool spots. Six of these patients underwent fluorescein angiography, in no case could fluorescein staining of vessel walls, fluorescein leakage, capillary closure, or macular changes be seen. Each of these patients had non-pulsatile retinal veins at the optic disc, ophthalmodynamometry suggesting that in every case venous pressure was at or just below diastolic 'ophthalmic artery' pressure.

Four patients had retinal veno-venous anastomoses indicating an earlier hemisphere retinal vein occlusion. No patient had a history of sudden loss of visual acuity. No patient had retinal haemorrhages. Each patient had non-pulsatile veins on the optic disc. Ophthalmodynamometry suggested a marked increase in retinal vein pressure to just below diastolic artery pressure in each case.

Discussion

INCIDENCE

Acute central retinal vein occlusion severe enough to produce visual symptoms is not infrequently associated with undiagnosed and/or 'not far advanced' glaucoma (Sugar, 1942; Braendstrupp, 1950; Vannas and Tarkkanen, 1960; Bertelson, 1961; Wise and others, 1971a). Asymptomatic central retinal vein occlusion is much more likely to be overlooked. The 2 per cent incidence of central and hemisphere retinal vein occlusion found in our series (cf. eight in 200 eyes found by Dobree (1957)), is probably spuriously low. The fact that no patient in this series was followed-up by the clinic from a known acute (haemorrhagic) central vein occlusion, is of interest. It might reflect a uniformly bad prognosis for all such patients in the clinic, progression to thrombotic glaucoma precluding their occlusion. It might also reflect their transfer to the Retinal Service of the hospital and subsequent loss to follow-up.

PRECIPITATING FACTORS

Many factors both systemic and local may decide whether, and at what stage of the glaucomatous disease, an eye with chronic simple glaucoma develops occlusion of the central retinal vein. Suggested factors include distortion at the laminar cribrosa (Behrman, 1962; Klein and Olwen, 1956; Emery, Landis, Paton, Boniuk, and Craig, 1974) and dystrophic changes in the wall of the central retinal vein (Verhoff, 1913; Salzman, 1939). Each of these factors may have contributed in our cases. Arterial disease has been considered an important factor (Hayreh, 1965, 1971; Paton, Rubenstein, and Smith, 1965). However, in our patients, ophthalmodynamometry did not reveal low 'ophthalmic artery' pressures, nor did fundoscopy reveal gross arterial disease.

Similar factors may be invoked in the pathogenesis of hemisphere vein occlusions; of special importance is the distortion of the affected vein along its course within an enlarged optic cup (Kohner and Shilling, 1976). It was not possible to identify the site of the obstruction in any of the four eyes with this type of retinal vein occlusion. Because of the difficulties in examining these particular patients, it was not possible to distinguish between upper and lower half retinal vein pressures at the optic disc (although this has been done with other patients). Similarly, in the one patient who underwent fluorescein angiography, it was not possible to determine which way, from upper to lower half of the retina or vice-versa, the venous blood flowed to circumvent the block.

CLINICAL FEATURES

Wise and others (1971b) ascribed the mild clinical picture of central retinal vein occlusion to a lack of functioning retina and reduced inflow of arterial blood. The identical clinical picture in eight eyes designated early-moderate glaucoma requires an alternative hypothesis. Kohner and Shilling (1976) when describing the clinical variations after acute thrombosis of the central retinal vein noted that mild cases undergo 'resolution'. According to these authors, 'mild' central retinal vein occlusions have few, if any, initial visual symptoms, the cotton-wool spots and haemorrhages disappear and retino-ciliary collateral channels develop at the optic disc. All except two eyes described in this paper fit into this category, 20 eyes showing resolution of central retinal vein occlusion, four eyes resolution of hemisphere vein occlusion. Only one patient (two eyes) was seen with retinal haemorrhages. Six eyes had readily recognizable retino-ciliary veins at the optic disc, four had veno-venous anastomoses draining blood away from the side of the obstructed 'hemisphere' vein, and the remainder had venous loops at the optic disc considered to indicate retino-ciliary collateral vessels. However, each patient had a marked increase in retinal vein pressure at the optic disc, to levels just below diastolic ophthalmic artery pressure. The development of bypass channels had *not* allowed return of a normal pressure differential between retinal artery and vein, and the obstruction to central and hemisphere retinal vein outflow must have persisted.

An alternative explanation for the mild clinical symptoms seen in our patients is retinal vein occlusion of gradual onset. If enlargement of the optic cup in chronic glaucoma with resultant distortion of its contained retinal veins is a major factor in pathogenesis, the occlusion would be slow and progressive with a gradual increase in retinal vein pressure. The concomitant elevation of intraocular pressure associated with glaucomatous cupping would ensure that there would be no marked increase in transmural hydrostatic pressure across small vessels from elevated vein pressure that might result in intraretinal haemorrhages. Long-standing increase in retinal vein pressure at the optic disc would allow time for the retino-ciliary collaterals of central vein occlusion and veno-venous collaterals of hemisphere vein occlusion to occur.

Although central or hemisphere retinal vein occlusion of gradual onset associated with chronic elevation of intraocular pressure would explain the clinical features in our patients, it is not possible to rule out a mild acute occlusive episode of any of them.

Eight patients were seen after their intraocular pressure had been brought under control, with a follow-up of one to four years. No patient was noted to have developed retinal haemorrhages after control of his intraocular pressure, as might be expected from the resultant increase in transmural hydrostatic pressure across small retinal vessels. This may reflect the comparatively slow reduction of intraocular pressure achieved by 'medical' means, it may also reflect changes in the retinal vascular system secondary to prolonged increase in retinal vein pressure. No patient showed signs of a further venous occlusive episode, and none had evidence for a marked worsening of his glaucoma (but five of the eight patients had end stage glaucoma when first seen). Every patient had persistence of the venous loops, retino-ciliary collaterals, and veno-venous anastomoses where previously noted. No patient had developed spontaneous pulsations of the central retinal vein, each showing persistence of elevated retinal vein pressure, although ophthalmodynamometry proved too inaccurate to say whether the retinal vein pressures had decreased. These unchanging features suggest persistence of the retinal vein obstruction throughout this follow-up period. To what extent the obstruction is reversible is unknown, but if related to distortion of the optic cup, it may be permanent. Unless the resistance of the new retinal vein outflow system diminishes abnormal vascular haemodynamics will persist. Elevation of retinal vein pressure reduces effective perfusion pressure of the inner retina and, probably, the optic disc (but cf. McLeod and Ring, 1976). Long-term reduction in perfusion, by affecting nutrition could affect function, and render the retina and optic disc more susceptible to the effects of any subsequent increase in intra-ocular pressure.

Summary

Asymptomatic chronic retinal vein occlusion that occurs in chronic simple glaucoma is described. The condition is characterized by marked elevation of retinal vein pressure with collateral vessels and vein loops at the optic disc in cases of central vein occlusion, or retinal veno-venous anastomoses along a horizontal line temporal and nasal to the disc in hemisphere vein occlusion. No patient had visible arterial changes, capillary closure, fluorescein leakage, or haemorrhages. The vein occlusion was not limited to 'end stage' glaucoma.

The role of increased intraocular pressure and glaucomatous enlargement of the optic cup with retinal vein distortion in the pathogenesis of the condition was stressed.

Follow-up of these patients revealed persistence of the retinal vein occlusion shown by elevated retinal vein pressures. This would reduce effective perfusion of the inner retina and optic disc and may affect the long-term visual prognosis.

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De novo lesions in presumed ocular histoplasmosis-like syndrome

STEVEN ABBOTT MILLER, THOMAS S. STEVENS, AND
GUILLERMO DE VENECIA
*From the Department of Ophthalmology, University of Wisconsin Hospitals,
University of Wisconsin, Madison, Wisconsin*

The presumed ocular histoplasmosis syndrome (POHS) has been amply described (Krill, Chishti, Klein, Newell, and Potts, 1969; Schlaegel, Weber, Halverston, and Keeney, 1967; Makley, Long, Usre, and Stephens, 1965; Maumenee, 1965; Gass, 1967; Woods and Wahlen, 1960; Krause and Hopkins, 1951; Van Metre and Maumenee, 1964; Schlaegel, 1975; Gass and Wilkenson, 1972) and in its complete form is characterized by five features:

1. A disciform macular lesion.
2. Multiple small punched-out choroidal atrophic lesions in the fundus periphery.
3. Peripapillary scarring.
4. Absence of inflammatory cells in the vitreous.
5. A positive histoplasmin skin test.

Many cases included in reports concerning this syndrome lack one or more of these features (Krill and others, 1969; Gass, 1967; Woods and Wahlen, 1960; Schlaegel, 1975; Braunstein, Rosen, and Bird, 1974).

Patients with a full-blown haemorrhagic disciform macular lesion in one eye frequently have one or more inconspicuous circumscribed white spots in the posterior pole of the fellow eye. Most observers believe that when a haemorrhagic disciform lesion arises in the second eye it does so from such a previously asymptomatic paramacular lesion (Krill and others, 1969; Schlaegel, 1975; Gass and Wilkenson, 1972; Smith, Knox, and

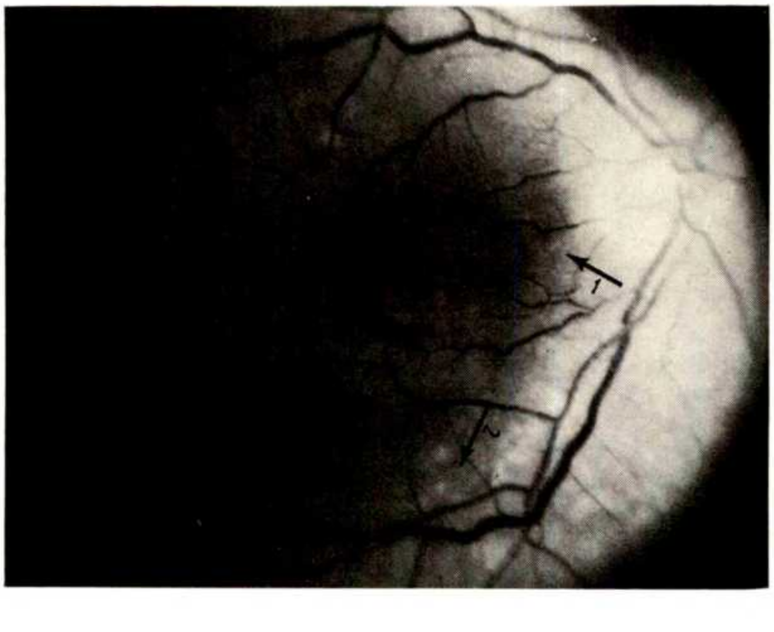

FIG. 1a. 2 *April* 1970. *Disciform macular lesion right eye. Centre subretinal greyish pink fibrovascular mounds surrounded by subretinal haemorrhage. Compare subtle choroidal lesions with fluorescein angiography (Fig.* 1b*) and follow-up photographs (Figs* 3a, b)

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Address for reprints: Steven Abbott Miller, MD, Department of Ophthalmology, University Hospitals, 1300 University Avenue, Madison, Wisconsin 53706, USA

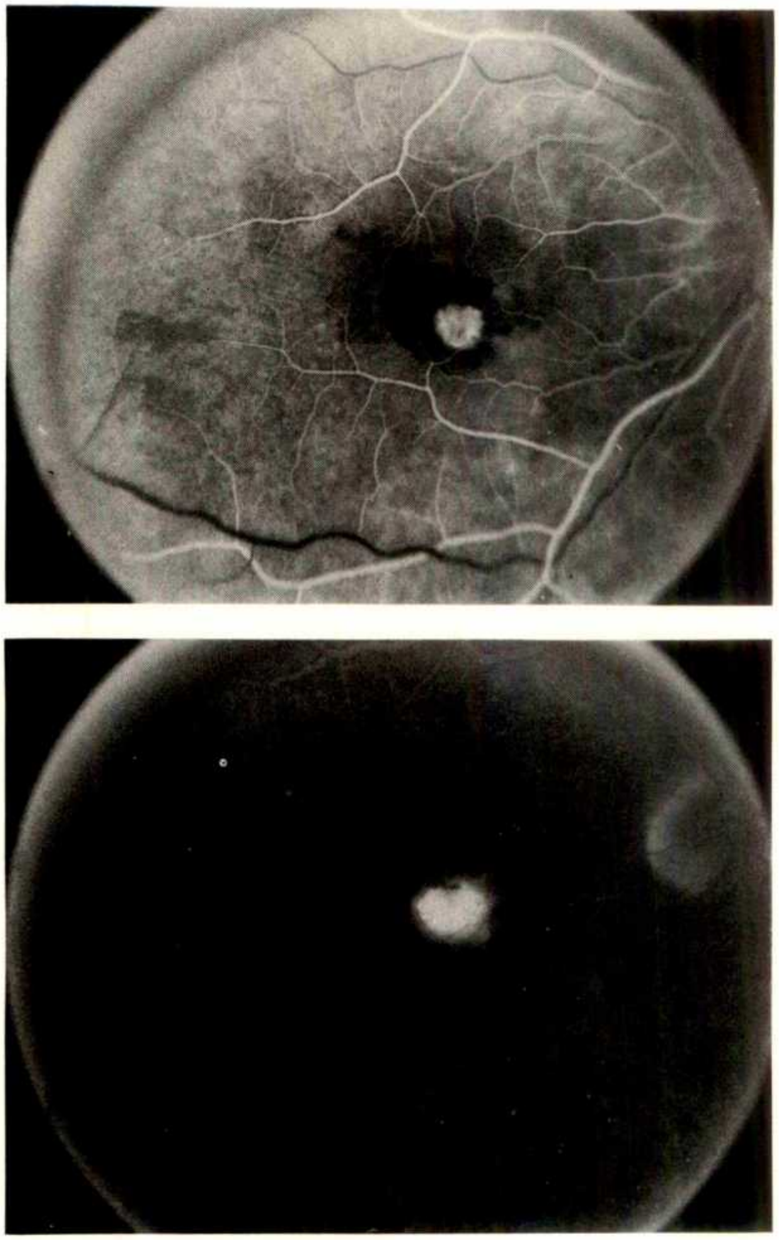

FIG. 1b, c *Fluorescein angiogram right eye on same day confirming presence of a subretinal neovascular membrane and showing retinal pigment epithelial window defects at site of arrows in Fig. 1 as well as two additional pigment epithelial defects temporal to fovea*

Jenson, 1973; Sawelson, Goldberg, Annesley, and Tomer, 1976). Fluorescein angiography is sometimes necessary to detect these lesions, which may be unapparent ophthalmoscopically (Krill and others, 1969; Gass and Wilkenson, 1972; Hyzarinen, Lerer, and Knox, 1971). Gass and Wilkenson (1972) have documented the development of a new *peripheral* lesion. Krill (1971) and Schlaegel (1972, 1974) have occasionally observed that typical macular disciform lesions develop in second eyes which had previously appeared normal ophthalmoscopically, but they have not reported such cases in detail. Recently, Ryan (1976) has reported a carefully documented case of de novo subretinal neovascularization in POHS.

In this report two cases are considered of multifocal choroiditis similar to or identical with POHS in which new lesions developed, at some time after an initial disciform process, in the retina which appeared normal ophthalmoscopically and

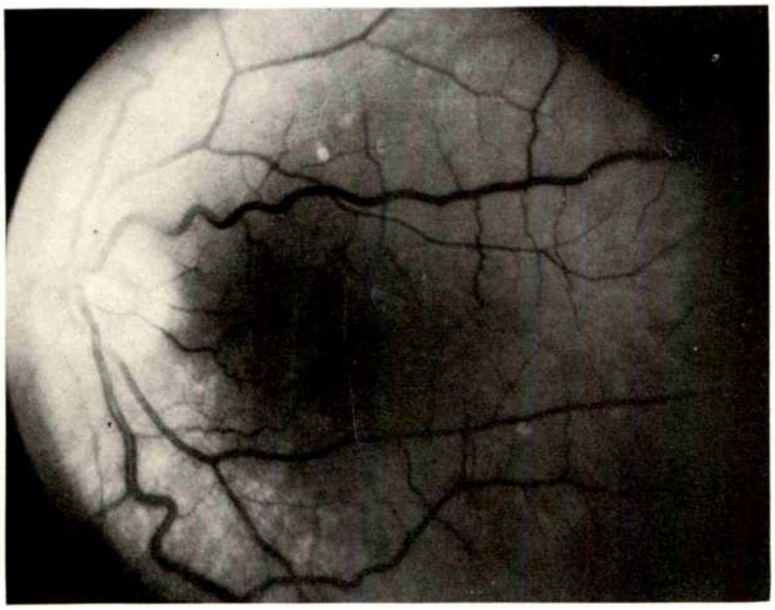

FIG. 2a 2 *April* 1973. *Black and white print from colour photographs of normal left eye*

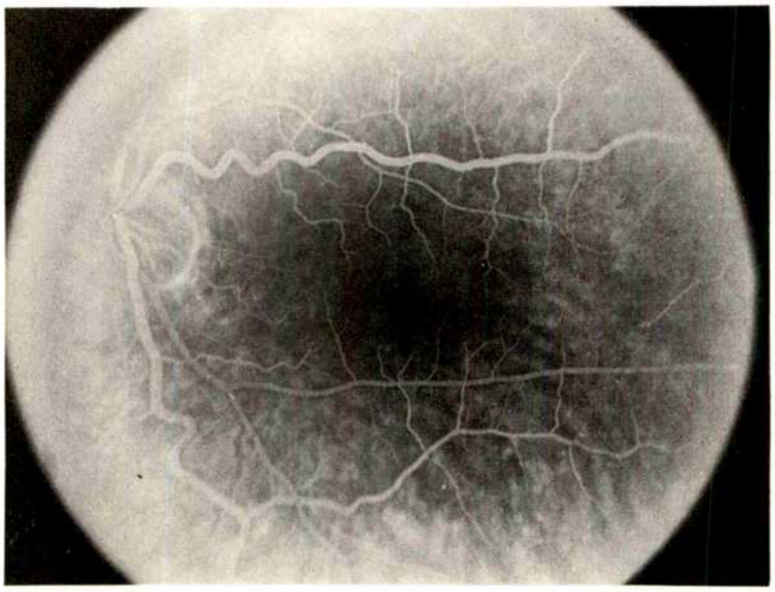

FIG. 2b 2 *April* 1973. *Normal fluorescein angiograms of left eye*

with fluorescein angiography. These 'de novo' lesions are documented as occurring not only in the initially involved eye, but also in the originally uninvolved eye.

Patients and methods

CASE REPORT 1

A 39-year-old White man who had been under heavy business pressure noted blurred vision shortly after accidentally striking his right brow against the edge of a cabinet. He was seen shortly after this event by his local ophthalmologist who diagnosed POHS, started him on oral prednisone, and referred him for consultation in three weeks' time.

On our initial examination on 2 April 1973, the visual acuity with correction was 20/50 right eye and 20/20 left. The refractive error was −7·25 + 4·00 axis 100 in the right eye and −7·50 + 3·50 axis 78 in the left. Slit-lamp biomicroscopy of the anterior segment and vitreous was normal. Both eyes demonstrated a narrow zone of de-

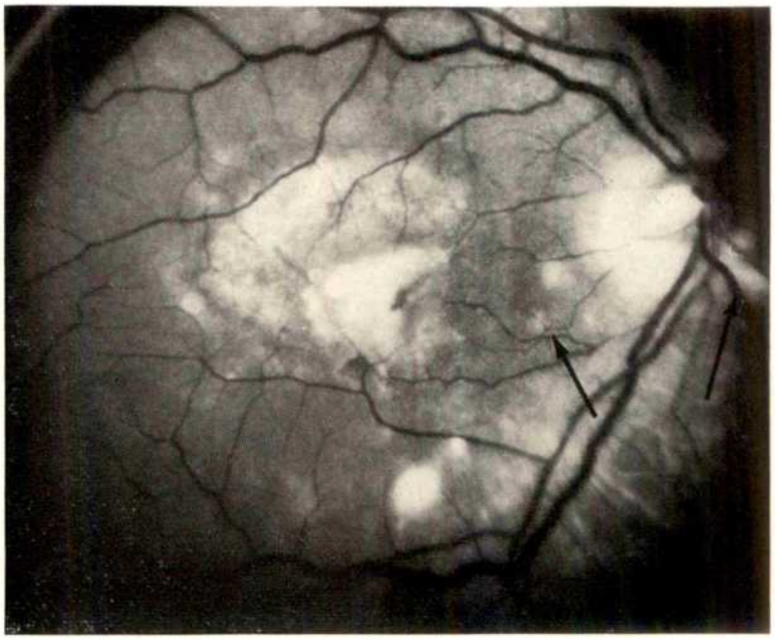

FIG. 3a 8 *August* 1975. *Hypertrophic macular scar right eye. Previous choroidal lesions are more distinct and new lesions are noted (arrow inferotemporal to disc indicates one such lesion). (Arrow inferonasal to disc points to distinct peripapillary activity)*

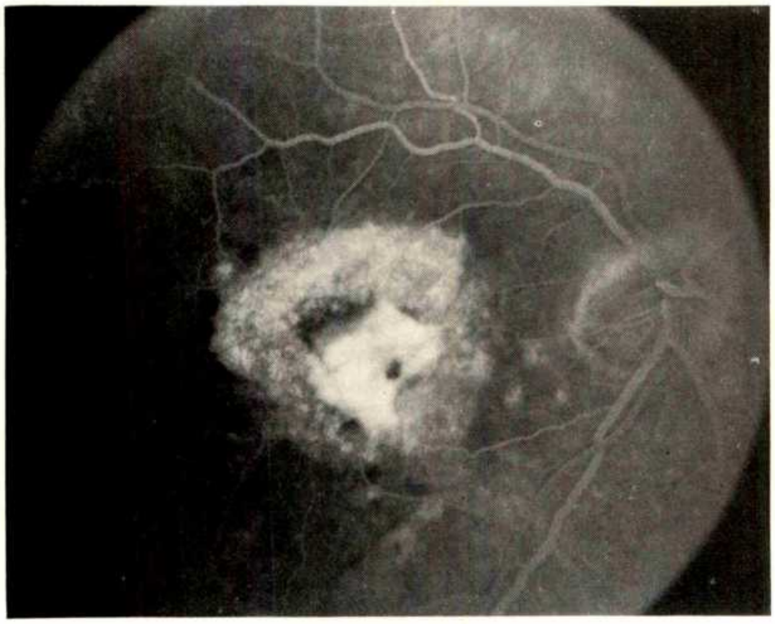

FIG. 3b 8 *August* 1975. *Fluorescein angiogram right eye confirms presence of previous subtle lesions and presence of new choroidal lesions*

pigmentation surrounding the disc. This was thought to represent a congenital myopic conus, although no other signs of myopic degeneration were present. Neither eye had peripheral atrophic lesions. Abutting the right fovea was a typical 'signet ring' lesion characterized by a roundish greyish to pinkish centre surrounded by dark 'pigment', which in turn was surrounded by a collarette of subretinal haemorrhage (Fig. 1*a*). Three small (less than 250 μm in diameter) circumscribed white spots were present, two in the perimacular area (Fig. 1 arrows) and one nasal to the disc. Fluorescein angiography confirmed the presence of subretinal neovascular membrane within the signet ring and a focal detachment of the overlying sensory retina (Figs 1*b*, *c*). Hyperfluorescence typical of retinal pigment epithelial defect was noted at these three sites as well as at two

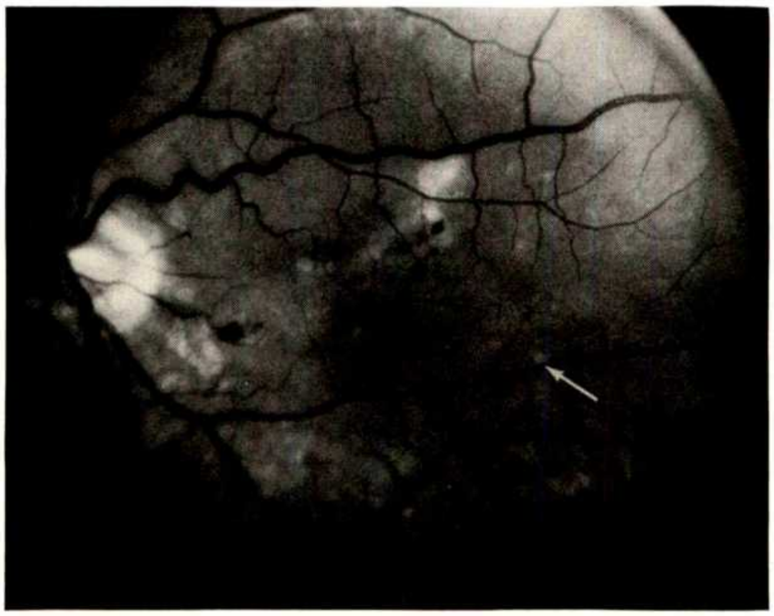

FIG. 4a 8 *August* 1975. *Left eye has a linear subretinal greyish membrane incompletely surrounded by subretinal and intraretinal haemorrhages. Other subtle lesions are present. (Example arrow)*

additional sites temporal to the macula (Figs 1*a*, *b*, *c*). Photography (Fig. 2*a*) and stereoscopic fluorescein angiography (Fig. 2*b*) performed on the left eye at that time showed a normal posterior pole.

Prednisone was gradually reduced and then discontinued, and the patient was followed-up by his local ophthalmologist. The patient was referred again on 8 August 1975. One week previously he had noted distorted vision and decreased visual acuity in his previously uninvolved left eye. Three days after the onset of symptoms, the referring ophthalmologist had again started the patient on prednisone. The visual acuity on 8 August was 8/200 in the right eye and 20/25 in the left. In the right eye there was a hypertrophic macular scar at the site of the original disciform lesion (Fig. 3*a*). There was depigmentation of the retinal pigment epithelium adjacent to this area. The three previously noted choroidal lesions were distinctly more prominent, and at least three additional choroidal lesions had appeared (Figs 3*a*, *b*). There was a definite peripapillary choroidal lesion inferonasally (Fig. 3*a* arrow). In the left eye there was a greyish subretinal lesion incompletely surrounded by subretinal and intraretinal haemorrhage (Fig. 4*a*). Subtle choroidal lesions were present (Fig. 4*a* arrow). Fluorescein angiography confirmed the presence of a subretinal neovascular membrane (Figs 4*b*, *c*). The lesion marked with an arrow in Fig. 4*c* is hypofluorescent in the early choroidal phase and normal fluorescent in the later phase. The patient was begun on systemic oral prednisone which was gradually reduced during the next three months. On 8 September 1975 the patient's visual acuity was 20/200 right eye and 20/60 left. The previously noted incomplete pigment ring and choroidal lesions were more predominant. The subretinal neovascular membrane network had partly coalesced. The choroidal lesions marked with an arrow in Fig. 4*a* fluoresced at this time (Fig. 5) as well as new areas of fluorescence (arrow). Additional lesions were present below the posterior arcade.

CASE REPORT 2

A 36-year-old White woman was seen by us on 12 December 1972. She stated that seven years previously she had noticed decreased vision in her left eye. She was initially seen at the University of Iowa Hospital where a diagnosis of chorioretinitis was made and was treated with systemic and topical corticosteroids with some improvement. A histoplasmin skin test was negative. Her symptoms recurred in the autumn of 1972, and she was seen at the Mayo Clinic where a histoplasmin test was positive. The diagnosis of recurrent chorioretinitis presumed to be due to histoplasmosis was made. The patient was given retrobulbar corticosteroids.

On our initial examination on 12 December the corrected visual acuity was 20/10 right eye and 20/60 left. Slit-lamp biomicroscopy of the anterior segment and vitreous was normal. At that time no peripheral atrophic scars were noted in either eye. Peripapillary changes were present in both eyes. The right macular region appeared normal (Fig. 6). In the left eye (Fig. 7) there was a chorioretinal scar just temporal to the fovea. A second subretinal scar surrounded by a zone of subretinal haemorrhage was noted inferotemporally. Overlying both scars was a serous detachment of the sensory retina. ('Atrophic' choroid spots (Fig. 7 arrow) are present within the posterior pole). The patient failed to return at that time for fluorescein angiographic studies.

On 27 June 1973 she returned because vision in her left eye had decreased. The visual acuity was 20/20 left

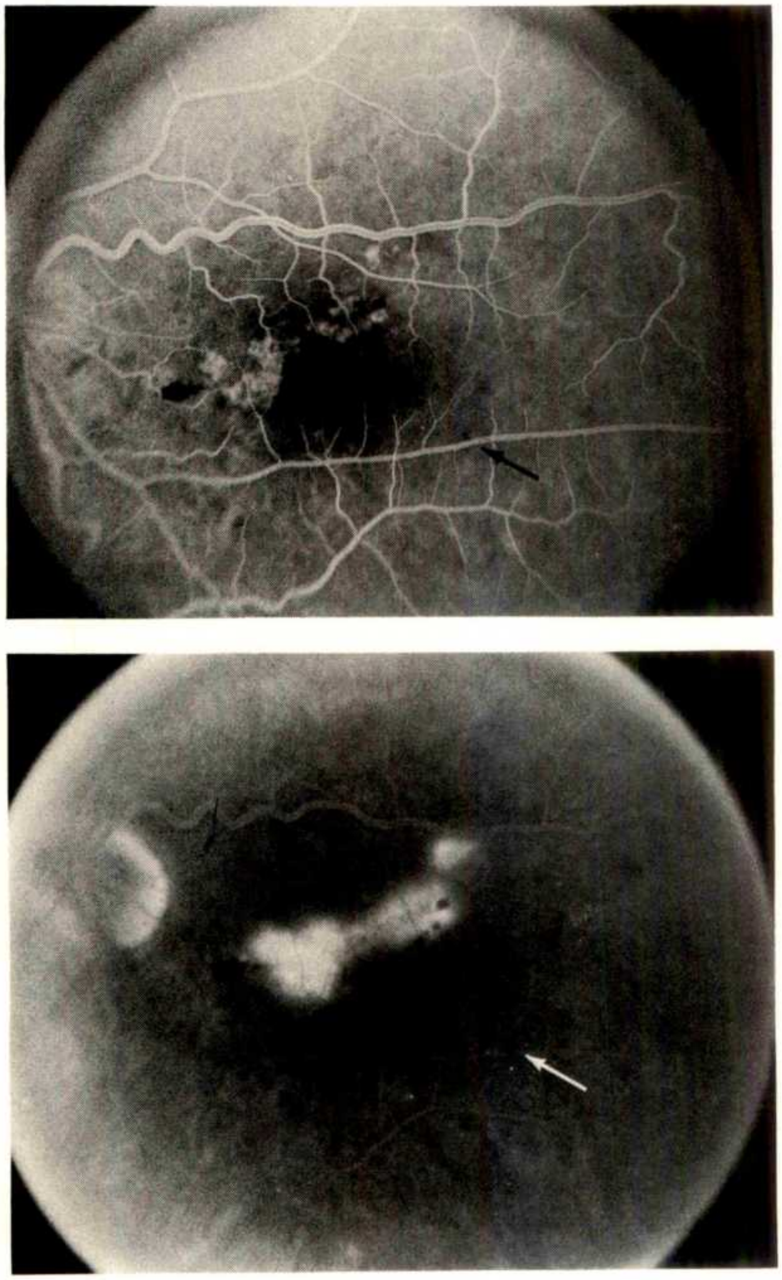

FIG. 4b, c *Case* 1, 8 *August* 1975. *Fluorescein angiogram left eye confirms presence of a subretinal neovascular membrane. Early phase angiography suggests several foci of subretinal neovascularization. The choroidal lesion in Fig.* 4a *is hyperfluorescent early and* (4b) *normal fluorescent in late stages*

eye and 20/200 right. No change in appearance of the right fundus was noted and stereo fluorescein angiography was normal (Fig. 8). In the left eye the subretinal haemorrhage had reabsorbed, and the subretinal fibrous tissue was now surrounded by an area of depigmentation. Fluorescein angiography (Figs 9*a*, *b*) showed a typical subretinal neovascular membrane with a prominent choroidal feeder and two cartwheel neovascular nets. There was minimal leakage from the subretinal neovascular membrane and subretinal space. Neither corticosteroids nor photocoagulation was thought to be indicated at that time.

The patient returned on 8 March 1975 with a three-day history of a central scotoma in the visual field of her right eye. The visual acuity was 20/15 right eye and 10/200 left. Four white spots (Fig. 10*a*) were noted near the right fovea. On fluorescein angiography window-type pigment epithelial defects were noted in three of

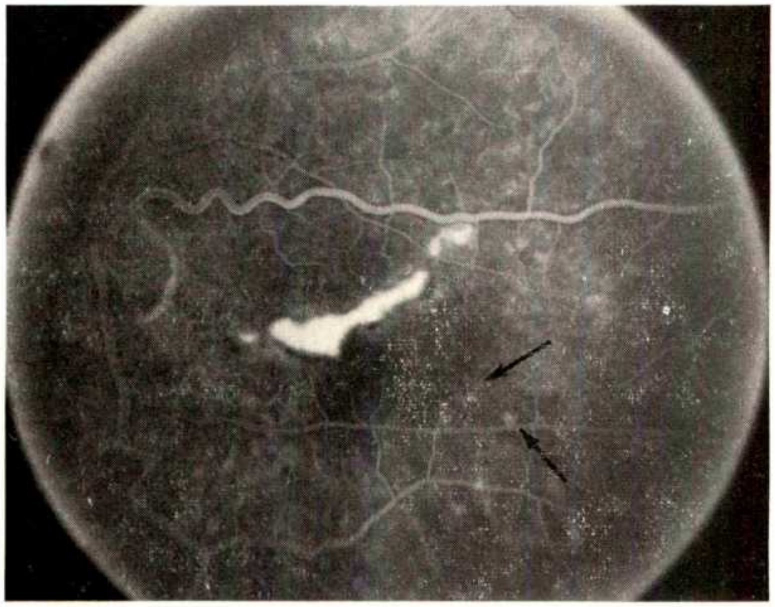

FIG. 5 *Case 1, 8 September 1975. Fluorescein angiography left eye showed tendency for lesion to coalesce. Previous choroidal lesion from Fig. 4a is now fluorescent as well as additional points of fluorescence (arrow Fig. 5)*

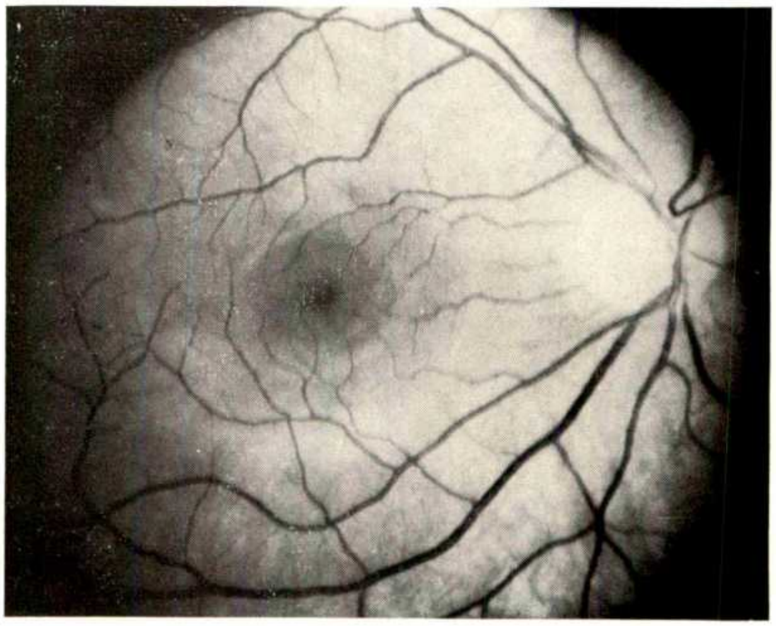

FIG. 6 *Case 2, 12 December 1973. Black and white print from colour photograph showed a normal-appearing macula (right eye)*

the four lesions, but the lesion immediately temporal to the fovea (Fig. 10*a* arrow) did not fluoresce (Fig. 10*b*). Metamorphopsia was noted on Amsler grid. No central defect could be demonstrated on the tangent screen. On 20 March the visual acuity was 20/15 right eye and 20/40 left. The patient was started on prednisone 50 mg every other day, but since her symptoms persisted despite a stable visual acuity, this was increased to 100 mg every other day. During the next four weeks, she continued to have symptoms. No scotoma could be demonstrated in the right eye with the 0 2E test object on the Goldmann perimeter. In the left eye there was a dense pericentral scotoma to the 5 4E test object. Colour vision was normal using the Farnsworth D-15 panel.

No reason could be found for the patient's persistent symptoms. Over the ensuing five months the prednisone was gradually reduced to 50 mg every other day and then maintained at that level.

On 8 August all four choroidal lesions were more

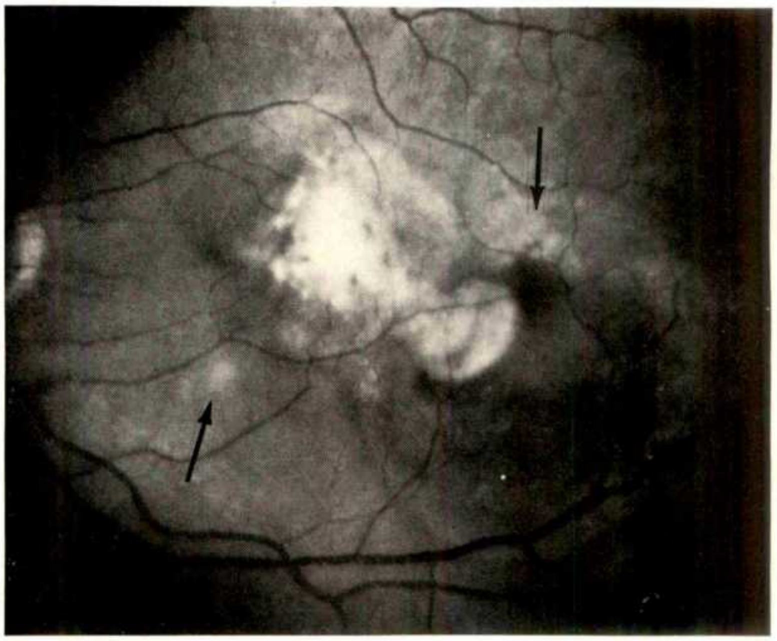

FIG. 7 *Case 2, 12 December 1973. (Left eye) chorioretinal scar just temporal to fovea. A small scar is present inferotemporally, partially surrounded by zone of subretinal haemorrhage. Not shown on the photograph is an overlying serous detachment of the sensory retina. 'Atrophic' choroidal scars (arrows) are present within posterior pole*

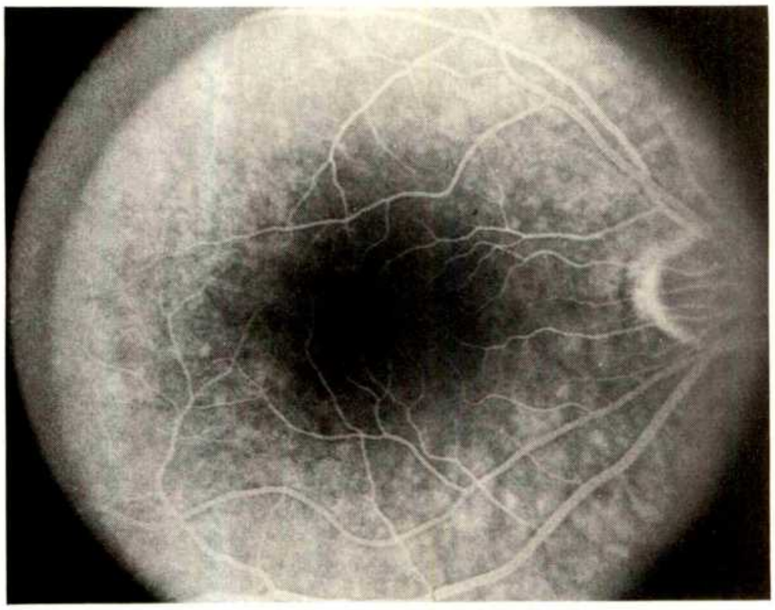

FIG. 8 *Case 2, 27 June 1973. Fluorescein angiography right eye shows no abnormalities except peripapillary scarring*

pronounced. Fluorescein angiography at this time showed, in addition to the three window-type defects present on 8 March, slight fluorescence of the lesion temporal to the fovea (Figs 11*a*, *b* compare with Figs 10*a*, *b*).

On 10 September 1975 visual symptoms had markedly lessened. A peripheral fundus examination repeated at this time showed four peripheral punched-out atrophic lesions in the right eye and no peripheral fundus abnormalities in the left. Fundoscopy examination on 12 November 1975 showed less prominence of the choroidal lesion temporal to the fovea in the right eye and no serous subretinal fluid in the left.

Discussion

The initial and later stereoscopic fluorescein angiography and fundus photograph findings are

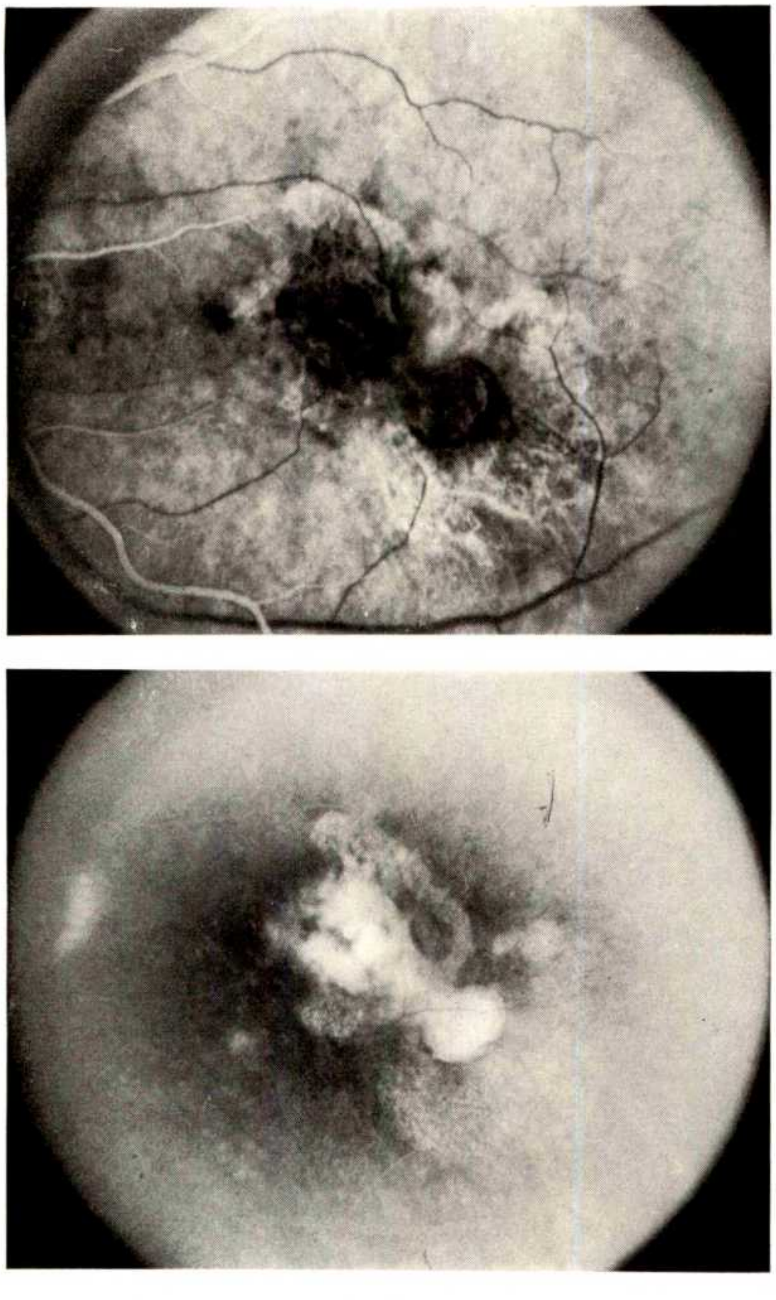

FIG. 9a, b *Case 2, 27 June 1973. Choroidal feeder left eye clearly visible to dumbell shape frond of subretinal neovascular membrane. Minimal subretinal fluid is not evident. There was surrounding area of depigmentation*

summarized in Table I. There are five points to consider in the cases (Table I).

PATIENT 1 initially had a subretinal neovascular membrane and a disciform process. He did not have 'peripheral' atrophic lesions, but rather circumscribed yellowish white spots within the posterior pole of the originally involved eye. He had peripapillary depigmentation thought to represent a congenital myopic conus. He did not have vitreous cells, and was not skin tested. This patient went on to develop subretinal neovascular membrane and a paramacular disciform process in his originally uninvolved eye that had been normal ophthalmoscopically and angiographically. He developed new choroidal white spots in the posterior pole in the originally involved as well as the un-

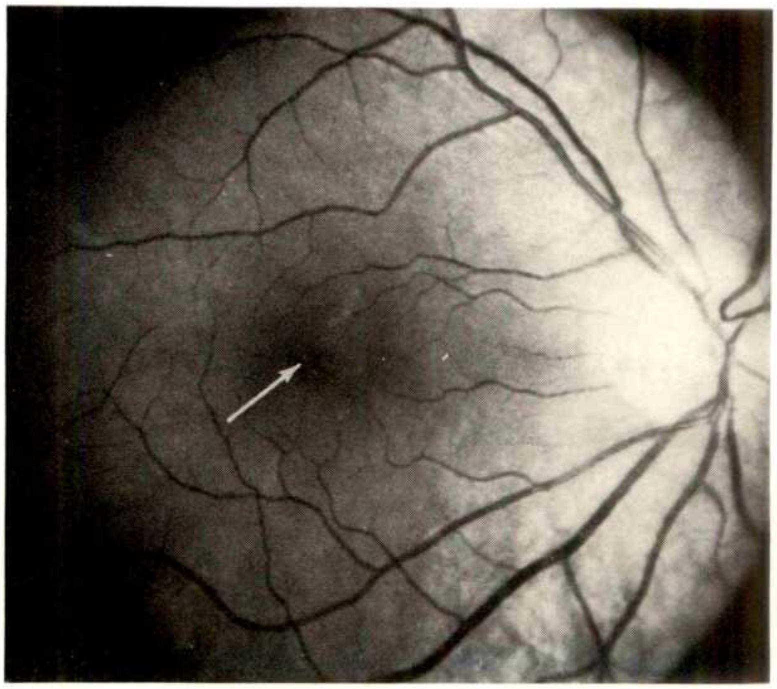

FIG. 10a *Case 2, 18 March 1975. Four small choroidal lesions now visible (right eye)*

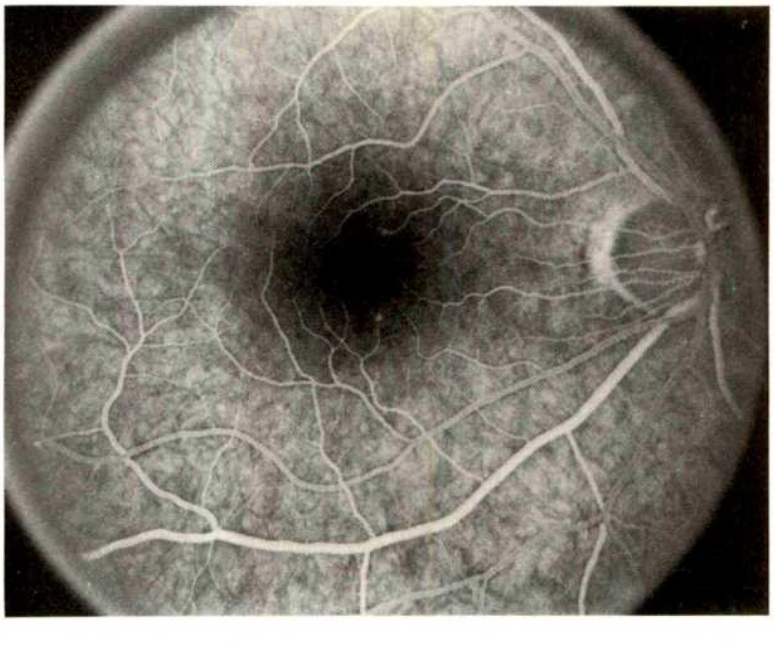

FIG. 10b *Case 2, 18 March 1975. Late venous phase fluorescein angiogram (right eye) shows retinal pigment epithelial window-like defects in two and perhaps three of four choroidal lesions. Lesion temporal to the fovea (see Fig. 10a arrow) does not fluoresce at this time, but does later (see Fig. 11b)*

involved eye, and he developed at least one definite peripapillary scar and some roughening of a presumed myopic conus.

PATIENT 2 initially had a subretinal neovascular membrane and a disciform process. She did not have peripheral atrophic lesions, but did have bilateral peripapillary scarring. She did not have inflammatory cells in the vitreous, and a histoplasmin skin test was negative. She went on to develop four choroidal white spots in the macular area of the originally uninvolved eye which had been normal ophthalmoscopically and angio-

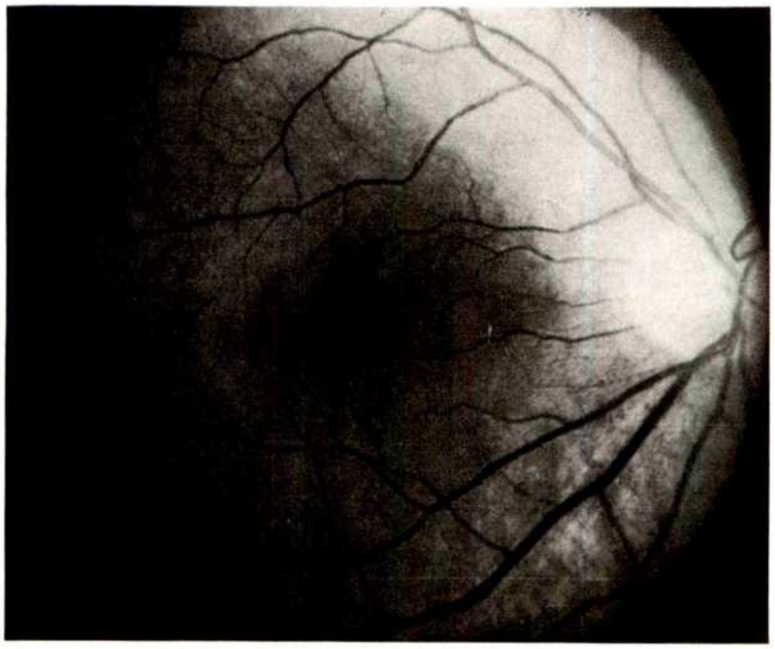

FIG. 11a *Case 2, 8 August 1975. Choroidal lesions (right eye) are more pronounced. Large round spot adjacent to fovea at 5 o'clock is a photographic artefact*

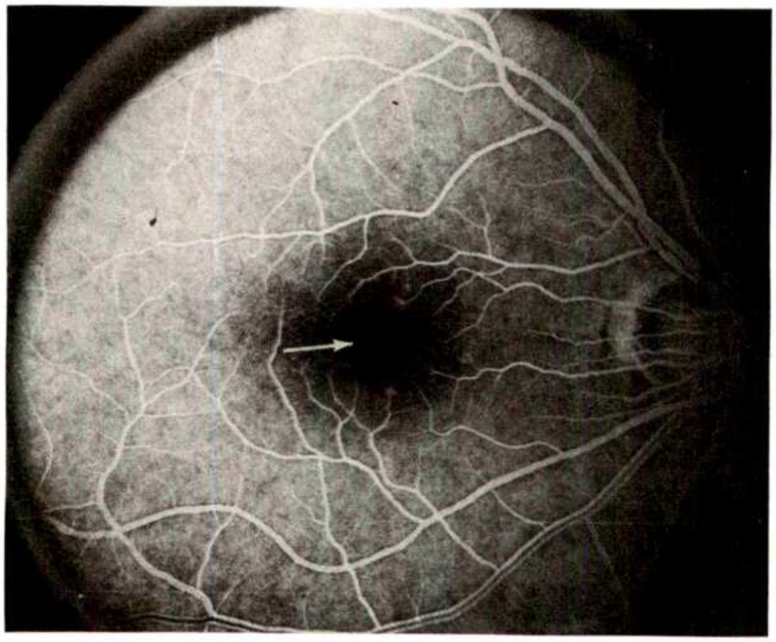

FIG. 11b *Case 2, 8 August 1975. Venous phase of fluorescein angiogram (right eye) shows, in addition to retinal pigment epithelial window-type defects of 8/75, slight fluorescence of the lesion temporal to the fovea (see Figs 10a, b)*

graphically. She also developed peripheral atrophic lesions in the originally uninvolved eye, and her histoplasmin skin test became positive.

The age, race, sex, geography, emotional or physical stress, and bilaterality represented by these two cases of POHS are consistent with those factors described in large surveys as typical of POHS (Krill and others, 1969; Schlaegel and others, 1967; Makley and others, 1965; Maumenee, 1965; Gass, 1967; Woods and Wahlen, 1960; Krause and Hopkins, 1951; Van Metre and Maumenee, 1964; Schlaegel, 1975; Gass and Wilkenson, 1972).

Both patients are middle-aged Caucasians living near the Mississippi River who relate a history of

Table I *Summary of cases. Initial presentation and findings on follow-up examination*

	Case 1		*Case* 2	
Symptom	*Originally involved eye*	*Originally uninvolved eye*	*Originally involved eye*	*Originally uninvolved eye*
Subretinal neovascular membrane				
Initial	Present	Not present	Present	Not present
Later	Present	Present	Present	Not present
Atrophic white spot				
Central 30°				
Initial	Present	Not present	Present	Not present
Later	Present	Present	Present	Present
Peripherally				
Initial	Not present	Not present	Not present	Not present
Later	Not present	Not present	Not present	Present
Peripapillary atrophy				
Initial	Questionable	Questionable	Questionable	Questionable
Later	Present	Questionable	Present	Questionable
Vitreous cell				
Initial	Not present	Not present	Not present	Not present
Later	Not present	Not present	Not present	Not present
Histoplasmin skin test				
Initial	Not done	Not done	Not present	Not present
Later	Not done	Not done	Present	Present

Table II *'Classic' POHS. Percentage of reported series conforming to classic POHS and variation in macular findings*

Demography	
Age	4th decade
Race	Caucasian
History of emotional or physical stress	Present
Region	Mississippi Valley
Macula of second eye	
Macular involvement initially (all forms)	56 to 67 per cent
Asymptomatic atrophic spot initially	24 to 36 per cent
Activation of atrophic spot on fundoscopy	20 to 24 per cent
Involvement on fundoscopy initially normal	0 to 2 per cent
Peripheral spots	Multiple (greater than 5) posterior to equator or in peri-equatorial zone
New spots	Rarely
Peripapillary lesions in one or both eyes	70 to 85 per cent
Histoplasmin skin test	
America	90 to 100 per cent
England	0 per cent

emotional and/or physical stress. Both have bilateral involvement with severe loss of visual acuity associated with haemorrhage in at least one eye.

There are several exceptions and variations noted in the reporting of the POHS (Table II). First, some reports, especially earlier ones, have included cases with some vitreous cells. Secondly, 10 per cent of American cases and virtually all British ones have a negative skin test (Braunstein and others, 1974). Thirdly, at least 25 per cent of patients do not have peripapillary scarring (Schlaegel and others, 1967; Schlaegel, 1974). Fourthly, epidemiological surveys attempting to characterize peripheral atrophic choroidal scars (Krause and Hopkins, 1951) in POHS have greatly clarified the appearance of these spots. Yet there are no rigid criteria for *(a)* 'peripheral' (? extra macular, posterior pole, equator, etc.), *(b)* number of lesions and appearance of these spots. Not surprisingly inclusive criteria in various reports range from 'every patient had more than one lesion' to 'typical findings' of POHS.

The reader at this point has decided whether he or she accepts both, neither, or one of the cases as 'presumed ocular histoplasmosis syndrome', an unrecognized form of retinal pigment epitheliopathy, or multifocal choroiditis of unknown aetiology. The most significant observations in these two cases are the occurrence of new choroidal lesions in the previously uninvolved eye as documented ophthalmoscopically and by fluorescein angiography, the development of new choroidal lesions within the originally involved eye, documentation and early evolution of the initial 'basic lesion' (Figs 4, 5, 10, and 11 arrow), and the need for angiography for visualizing underlying choroidal lesions.

Patients with POHS-like lesions in one eye and a normal posterior fundus in the other should not be given an unequivocally good prognosis for the second eye.

Summary

Two patients with multifocal choroiditis similar or identical to POHS are presented. Colour photographs and fluorescein angiography document the occurrence of de novo lesions in the originally involved eye. The cases also demonstrate the development of new choroidal lesions within the originally involved eye, the early evolution of the 'basic choroidal lesion', and the need for fluorescein angiography for visualizing the underlying choroidal lesion.

Addendum

Since submitting this paper Wilkinson (1976) has documented the appearance of de novo lesions in presumed ocular histoplasmosis. Cleasby (1976) has reported on 20 patients with neovascular membranes resembling those seen in POHS, but without any associated characteristic ophthalmoscopic findings considered necessary to make a diagnosis of POHS.

We thank Dr Alan A. Ehrhardt for referring one of the patients and Dr M. D. Davis for his guidance in preparing this manuscript.

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Treatment of peripheral corneal ulcers by limbal conjunctivectomy

FRED M. WILSON II, MERRILL GRAYSON, AND FORREST D. ELLIS
From the Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana

Peripheral corneal ulcers can still pose difficult clinical problems despite therapeutic advances such as specific antimicrobial agents, collagenase inhibitors, heparin, ocular lubricants, biological adhesives, and soft contact lenses. This paper reports the healing of several types of progressive marginal ulcers after the excision and recession of adjacent limbal conjunctiva (limbal conjunctivectomy), in some cases after other modes of treatment had been unsuccessful.

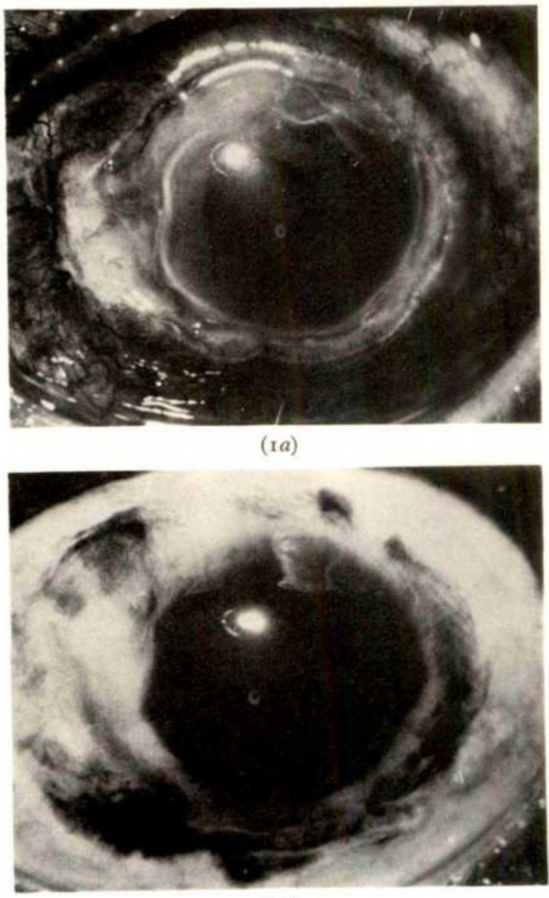
Case reports

CASE 1, MOOREN'S ULCER

A 54-year-old Black woman developed a severely painful, largely non-infiltrative ulcer of the nasal left cornea. The ulcer had an overhanging central edge and progressed circumferentially during a period of one year to involve nearly the entire corneal periphery (Fig. 1*a*). Progression occurred despite treatment at various times with acetylcysteine drops, L-cysteine drops, topical and subconjunctival heparin, artificial tears, soft contact lens, a short trial of topical corticosteroids, and a trial without any treatment to minimize the possibility of overtreatment. Two years before we saw her, the patient had lost her other eye from a similar process despite heparin treatment and lamellar keratoplasty; the eye had been enucleated to relieve severe pain, although the ulcer had not perforated.

Ocular cultures and scrapings were negative or non-contributory. Extensive systemic examinations by internal medicine were negative on two separate occasions except for sporadic increases in immunoglobulins M and A. No other evidence was found to indicate the presence of autoimmune disease.

After all other therapeutic attempts had failed, we performed a 360° peritomy and made contiguous cryoapplications to the central and peripheral edges of the ulcer. The cryotherapy was performed with an Amoils cryosurgical retinal probe which reached temperatures of −40 to −50°C. Each application was maintained for 10 to 15 seconds. Fibrous tissue began to appear within the ulcer about one week later, followed in a few days by superficial vascularization. The ulcer had healed and epithelialized three weeks after surgery (Fig. 1*b*) and L-cysteine and heparin drops were continued for three weeks after it had healed. The ulcer has


(1*a*)

(1*b*)

FIG. 1 *(Case 1)*. (a) *Mooren's ulcer just before surgery. All medical treatment had failed to halt progression.* (b) *Complete healing of ulcer after peritomy and cryotherapy to ulcer edges*

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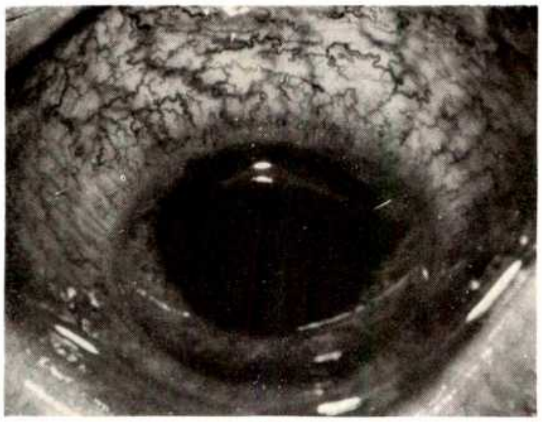
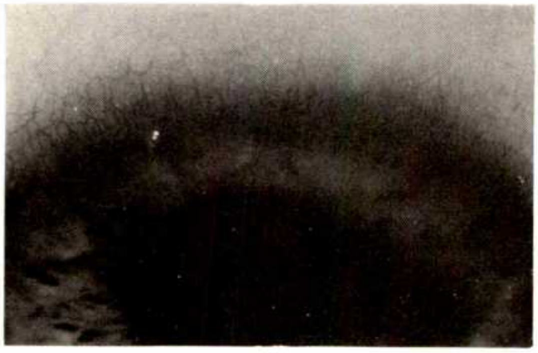
Address for reprints: Fred M. Wilson II, MD, 1100 West Michigan Street, Indianapolis, Indiana 46202, USA



(2*a*)



(2*b*)

FIG. 2 *(Case 2).* (a) *Marginal ulcer of gonococcal keratoconjunctivitis after treatment elsewhere with topical corticosteroid-sulphonamide. Subsequent treatment with systemic penicillin, topical bacitracin, and topical L-cysteine produced bacteriological cure, but ulcer persisted.* (b) *Ulcer healed* 10 *to* 14 *days after limbal conjunctivectomy with recession*

remained healed for more than three years except for several minor erosive recurrences for which the patient has been given short courses of L-cysteine.

CASE 2, GONOCOCCAL KERATOCONJUNCTIVITIS

A 25-year-old White woman developed purulent conjunctivitis of the left eye three weeks before examination. The discharge diminished considerably after she was given a topical corticosteroid-sulphonamide preparation by a non-ophthalmic practitioner, but mild discharge and redness persisted.

Examination showed lid swelling, papillary conjunctivitis, scant mucopurulent discharge, and no lymphadenopathy. Just inside the superior limbus there was a non-infiltrative corneal ulcer, extending nearly to Descemet's membrane in some areas (Fig. 2*a*). Corneal sensation was normal.

Conjunctival scrapings revealed Gram-negative diplococci, mostly extracellular, with moderate numbers of polymorphonuclear leucocytes (PMNs). Cultures with fermentation tests confirmed the presence of ocular (and genital) *Neisseria gonorrhoeae*.

The corticosteroid-sulphonamide ointment was stopped, and treatment with systemic penicillin, topical bacitracin ointment, and L-cysteine drops was begun.

Six days later the eye was essentially white and repeat cultures were negative, but the ulcer was not improved and was thought to be deeper in some areas. We then excised a 4 to 5 mm strip of limbal conjunctiva adjacent to the ulcer and loosely recessed (without sutures) the remaining conjunctiva to a distance of about 1 cm from the limbus. The bacitracin and L-cysteine were discontinued. The ulcer showed early fibrosis three days after surgery and was healed and epithelialized 10 to 14 days after the procedure (Fig. 2*b*). The ulcer has remained healed for two years.

CASE 3, RHEUMATOID ARTHRITIS

A 64-year-old White woman had had severe, immobilizing rheumatoid arthritis for 17 years. Her general medications were salicylates, indomethacin, and ironized yeast. For six weeks she had complained of bilateral ocular discomfort and blurred vision, for which she was given an unknown eyedrop which provided slight and temporary symptomatic improvement.

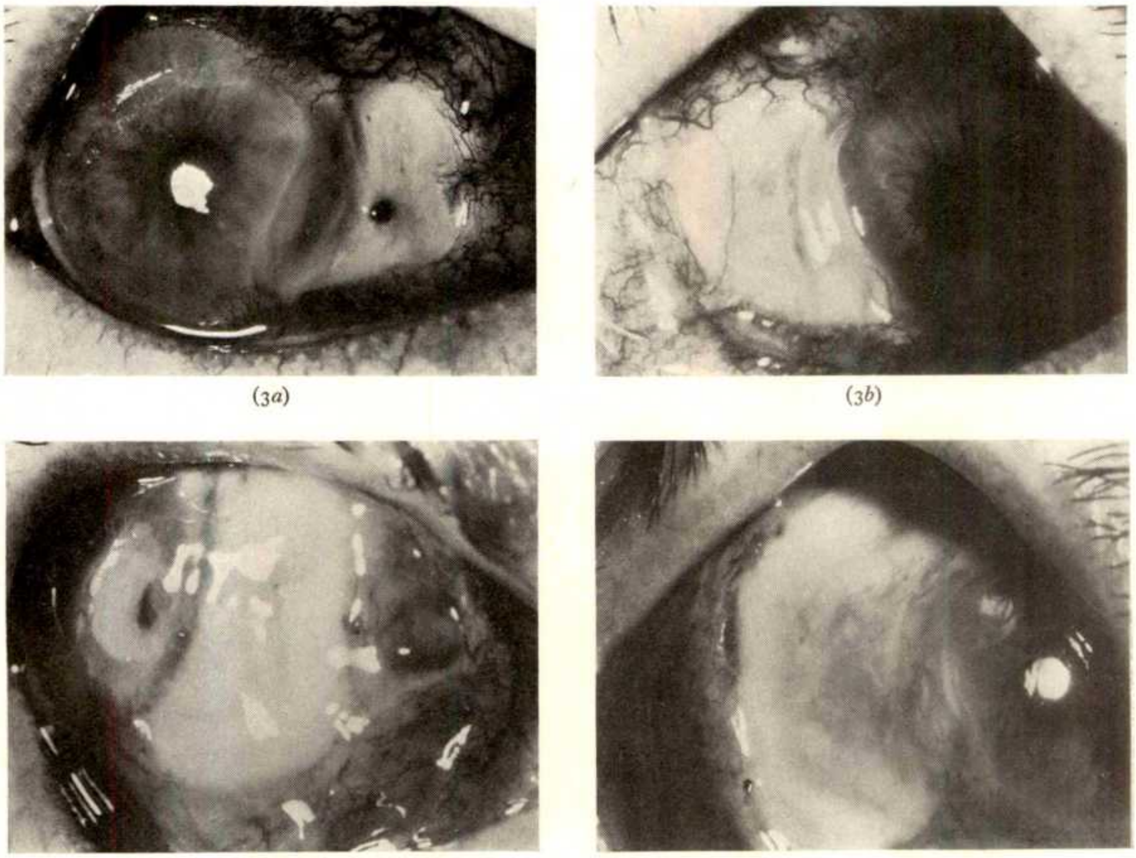
Corneoscleral ulcerations, extending to about two-thirds of the corneoscleral thickness, were present bilaterally, nasally in the right eye (Fig. 3*a*) and nasally and temporally in the left eye (Fig. 3*b*). The ulcerations were essentially non-infiltrative, and there was no discharge. The eyes were not dry. Slit-lamp examination was not possible, but the anterior chambers were grossly clear.

Significant laboratory studies included radiological changes of rheumatoid arthritis, slightly decreased serum albumin, raised serum gamma globulin, raised serum immunoglobulins G and M, positive rheumatoid factor, and lupus erythematosus phenomenon (LE prep.), 2+ 'speckle' positive fluorescent antinuclear antibody, increased erythrocyte sedimentation rate, and normochromic normocytic anaemia by bone marrow examination.

We began ocular treatment for both eyes with L-cysteine drops, sulphacetamide drops, and artificial tears. Nine days later the ulcers were larger and deeper, and it was feared that perforation might be imminent. Two weeks after beginning our treatment bilateral conjunctivectomy with recession was performed adjacent to the areas of ulceration. Much of the excised conjunctiva was bulbar rather than limbal, since the ulcers extended on to the sclera. Postoperatively L-cysteine was stopped, but sulphacetamide and artificial tears were continued. A fibrinous coagulum was apparent over all areas of ulceration four days after surgery: some of this material appeared to become fibrous six days after surgery. After eight days both eyes were healing well (Figs 3*c*, *d*), and the patient was discharged. Healing was soon complete, and there has been no recurrence during the subsequent two years.

CASE 4, KERATOCONJUNCTIVITIS SICCA

This 72-year-old White woman had been followed-up for two years for dry eyes in association with xerostomia



(3*a*) (3*b*)

(3*c*) (3*d*)

FIG. 3 *(Case 3)*. (a and b) *Severe bilateral corneoscleral ulcerations in patient with rheumatoid arthritis. Topical L-cysteine and artificial tears produced no improvement.* (c and d) *Eight days after conjunctivectomy with recession all ulcerations show healing with fibrinous and fibrous tissue. White areas of sclera appear larger only because more bare sclera is visible after conjunctival excision. Complete healing ensued*

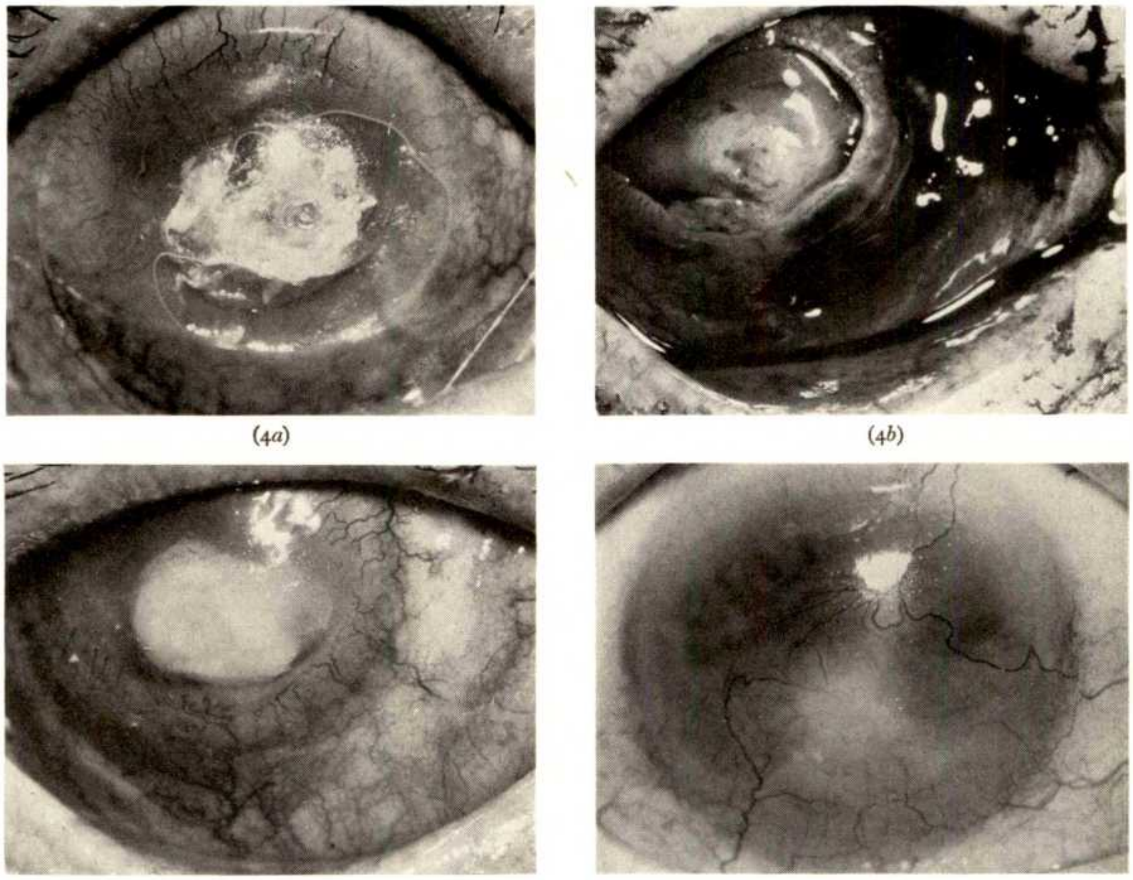
and rheumatoid arthritis (Sjögren's syndrome). Artificial tears alone were insufficient; bilateral soft contact lenses were prescribed for full-time wear in conjunction with sulphacetamide drops and artificial tears. A diffuse cellular infiltration of the superficial stroma of each cornea appeared four days later. The lenses were discontinued, and treatment with topical gentamicin and bacitracin ointments and artificial tears was started. Small central epithelial defects developed bilaterally six days later. The left eye healed and its infiltrate cleared, but the right cornea suddenly perforated centrally. We applied cyanoacrylate glue and another soft contact lens (Fig. 4*a*), and the anterior chamber re-formed within minutes. The glue detached 10 days later, revealing a raised, vascularized scar over the site of perforation, but a large non-infiltrative ulceration developed along the entire nasal limbus (Fig. 4*b*).

Limbal conjunctivectomy with recession was performed (Fig. 4*b*), and a fibrinous coagulum with fine vascularization began to fill the defect two days later. L-cysteine, artificial tears, and the soft lens were continued for a few more days. The eye healed (Fig. 4*c*) and has remained stable for 14 months. The corneal scarring and surface irregularities have cleared considerably (Fig. 4*d*).

CASE 5, ROSACEA

A 63-year-old White man was seen for a non-infiltrative ulcer of the inferotemporal periphery of the left cornea (Fig. 5). After onset about one month previously, he had been treated elsewhere with a topical corticosteroid-sulphonamide ointment for an unknown length of time. There was no history of rheumatoid arthritis or other autoimmune disease.

The typical findings of rosacea were present on the face—that is, erythema, papules, pustules, and telangiectases without comedones. There was clinical evidence of mild staphylococcal blepharitis bilaterally. Rosacea keratoconjunctivitis was present as shown by



(4*a*) (4*b*)

(4*c*) (4*d*)

FIG. 4 *(Case 4).* (a) *Cyanoacrylate adhesive and soft contact lens sealing corneal perforation in Sjögren's syndrome.* (b) *Adhesive has detached* 10 *days later revealing underlying scar. Marginal corneal ulceration has appeared along nasal limbus, and conjunctivectomy with recession has been performed.* (c) *Marginal ulcer healing* 10 *days after conjunctivectomy.* (d) *Final result seven months later*

dilated conjunctival vessels and peripheral vascularization of the cornea, worse below. The ulcer penetrated to slightly more than half of the stromal thickness.

Conjunctival scrapings were negative. Lid-margin cultures revealed a few colonies of *Staphylococcus epidermidis.*

We began treatment with topical acetylcysteine drops, lid scrubs, and bacitracin ointment to the lid margins. The referring physician performed limbal conjunctivectomy with recession, and the ulcer healed in about 10 days. No further ulceration has occurred in the succeeding one year.

CASE 6, THERMAL BURN

A 30-year-old Black man sustained first, second, and third-degree burns on the chest, face, and both eyes, from molten metal. The left eye was destroyed. The right cornea was opaque, and there was extensive conjunctival ischaemia and necrosis, worse below.

The left eye was eviscerated. The right eye was treated with topical antibiotics and cycloplegia, daily lysis of symblepharons, and the insertion of a plastic scleral shell for maintenance of the fornices. Two weeks later a marginal corneal ulcer appeared inferonasally. Topical acetylcysteine drops were started, but the ulcer deepened. Perforation was feared, so limbal conjunctivectomy with recession was performed one week after onset of the ulcer. Acetylcysteine drops were continued. Vascularization of the ulcer appeared within 10 days, and it was healed 19 days after the surgery. There has been no recurrence of ulceration.

CASE 7, RHEUMATOID ARTHRITIS

A 70-year-old White man had had rheumatoid arthritis for 40 years, for which he was taking only aspirin. One week before our examination he developed foreign-body sensation and photophobia of the right eye. No ocular treatment had been given.

We found a relatively quiet, non-infiltrative, ovoid, paralimbal ulcer superonasally; it extended to slightly more than half of the stromal thickness. There was mild hyperaemia and extension of the adjacent limbal vascular arcades. The anterior chamber showed 1+ flare and cells without keratic precipatates.

We performed limbal conjunctivectomy with recession and started topical L-cysteine drops. Two days later the ulcer had partially filled in coincident with further extension of the limbal vessels. We continued L-cysteine, and healing and vascularization progressed. Three weeks after beginning treatment the ulcer was healed without staining (Fig. 6), and it has remained stable over the intervening four months.

CASE 8, ULCER AFTER CATARACT SURGERY (POSSIBLE MOOREN'S ULCER)

An 81-year-old White woman had a slightly infiltrative marginal corneal ulcer in the area of interrupted catgut sutures which had been placed at the time of cataract surgery in the left eye, four months earlier. The referring ophthalmologist had previously tried treatment with topical corticosteroids and patching without success.

The ulcer extended from 10 to 2.30 o'clock superiorly and to about half of the stromal thickness. Treatment was begun with topical acetylcysteine and sulphacetamide drops, but one month later the ulcer was not improved. We then advised limbal conjunctivectomy with recession. This was performed by the referring ophthalmologist about one month later, at which time the ulcer had extended to the 7.0 o'clock position nasally and to the 5.0 o'clcock position temporally. The procedure produced minimal or no improvement. The patient subsequently was treated elsewhere with placement of a conjunctival flap that also became involved in the ulcerative process, and finally with a graft of mucous membrane in conjunction with lamellar shaving of the remaining central island of corneal tissue. She has since been lost to follow-up.

Histopathology

All of the excised strips of conjunctiva showed moderate to large numbers of mononuclear cells and smaller numbers of PMNs infiltrating the subepithelial tissues. The mononuclear reactions consisted mainly of lymphocytes, although scattered monocytes were also present. All specimens except those from the case of rosacea (Case 5) and the thermal burn (Case 6) also contained moderate to large numbers of plasma cells; Case 5 did not contain plasma cells, and Case 6 had only rare ones. The conjunctiva from the case of ulceration after cataract surgery (Case 8) showed also scattered eosinophiles.

Conjunctiva was not available from the case of Mooren's ulcer (Case 1), but we were able to examine the patient's other eye, which had been previously enucleated. The subepithelial connective tissues and superficial sclera adjacent to the ulcer contained extensive infiltrates of lymphocytes and plasma cells, in about equal numbers, while the corneal ulcer itself showed only a few isolated lymphocytes.

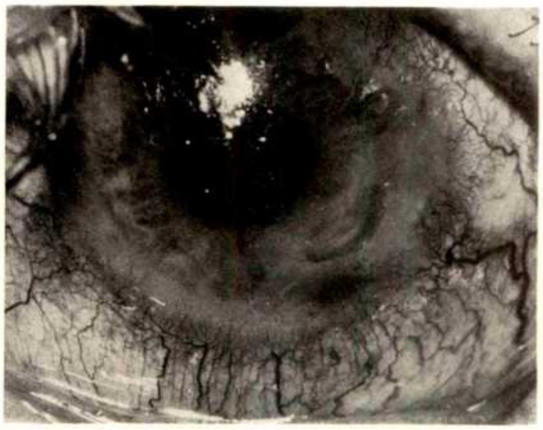


FIG. 5 *(Case 5). Corneal ulcer of rosacea keratoconjunctivitis. Healing occurred about 10 days after conjunctivectomy with recession. Topical acetylcysteine was used postoperatively*

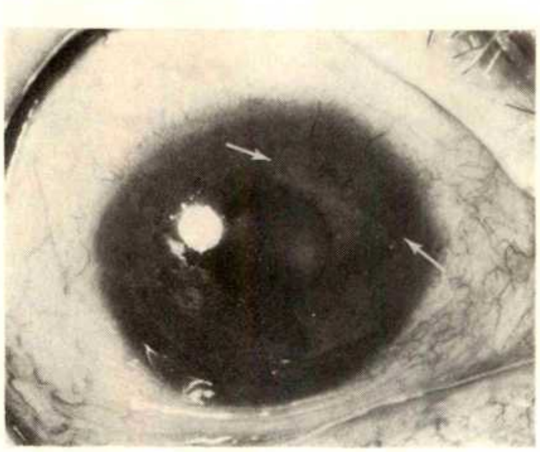


FIG. 6 *(Case 7). Healed marginal ulcer in patient with rheumatoid arthritis (ends of scar delineated by arrows). Healing was complete three weeks after conjunctivectomy with recession. Topical L-cysteine was used postoperatively*

Discussion

Aviel (1972) reported the successful treatment of four cases of Mooren's ulcer by the empiric use of peritomy and cryoapplications to the ulcer edges, prompting us to resort to the same treatment in our Case 1 after all others had failed. Healing was rapid and complete, with no recurrence over a period of more than three years.

There was no ready explanation for the apparently beneficial effect of this mode of therapy until Brown (1972) incriminated the conjunctiva as a source of collagenase and proteoglycanase, enzymes that are capable of causing corneal ulceration by producing destruction of corneal collagen and ground substance. Brown (1972) also suggested excision of limbal conjunctiva as a possible treatment for Mooren's ulcer and has since alluded to the apparently successful use of this treatment for rapidly progressing peripheral corneal ulcers and scleromalacia (Brown, 1974). We thus began to suspect that the successful outcome of our Case 1 may have been related more to peritomy and conjunctival recession than to cryotherapy. In all subsequent cases we have omitted cryotherapy and have substituted conjunctival excision for simple peritomy, with good results in all but one instance (Case 8). Whether cryotherapy has any value, alone or in combination with conjunctivectomy, remains to be determined.

Bloomfield and Brown (1974) confirmed the presence of, and partially characterized, a collagenase produced by both normal and inflamed rabbit conjunctiva. They thought that the conjunctival epithelium was the major source of the collagenase. They also cited unpublished studies in which they detected collagenase and proteoglycanase in conjunctiva adjacent to Mooren's ulcers.

The precise origin of conjunctival or corneal collagenase in any given clinical situation is uncertain. Epithelium in contact with wounded stroma (Brown and Weller, 1970), PMNs (Brown, Weller, and Akiya, 1970; Brown and Hook, 1971), and fibroblasts (Bloomfield and Brown, 1973) have all been found to be capable of producing collagenase under various experimental circumstances. Factors that may initiate collagenase production are also poorly understood. Presumably some immunological or traumatic stimulus calls forth and activates one or more of the above cell types. The presence of plasma cells and lymphocytes in the conjunctival tissues that were excised from our cases suggests that humoral or cellular immune phenomena are operative, although both of these cell types are not infrequently found in subepithelial conjunctival inflammation of various causes and may be non-specific findings.

While removal of proteolytic conjunctival enzymes or their cells of origin seems likely to be the means by which conjunctivectomy exerts its beneficial effect, this has not been proved. The fact that the procedure causes bleeding, and that serum is known to contain anticollagenase factors (Eisen, Bloch, and Sakai, 1970; Hook, Brown, Iwanij, and Nakanishi, 1971; Berman, Barber, Talamo, and Langley, 1973), must also be considered. Another possible explanation is that the surgical trauma simply stimulates vascularization, fibrosis, or other non-specific aspects of inflammation. If the elimination of conjunctival enzymes is critical, it may be important to ensure that the recessed conjunctiva does not grow to the limbus again before re-epithelialization of the corneal ulcer. In some cases the recessed conjunctiva may need to be sutured to the sclera well posterior to the limbus as is done in the bare-sclera technique of pterygium surgery.

We do not advocate conjunctivectomy with recession as primary treatment of every case of marginal corneal ulceration. That the procedure is not a panacea is clearly demonstrated by its failure in Case 8 above. Moreover, marginal ulcers comprise a heterogeneous group of diseases, and many cases respond well to other modes of treatment. Some types are self-limited and do not require specific or enthusiastic therapy. A clinical classification of marginal ulcers, which we have found to be useful, is given in the Table. The superficial infiltrative ulcers are normally self-limited or respond well to topical treatment with antibiotics or corticosteroids. Corticosteroids are generally effective for the non-infectious types of deep infiltrative ulcers, whereas these drugs tend to worsen most of the ulcers of the deep non-infiltrative group, probably because of corticosteroid enhancement of collagenase activity. It is this last group that seems to respond best to the use of collagenase inhibitors, but not invariably so, and Mooren's ulcer is notorious for frequently resisting all medical treatment. The results of conjunctivectomy appear to be encouraging for this deep non-infiltrative group, but we have had no experi-

Table *Typical clinical characteristics of peripheral corneal ulcers**

Ulcer	*Infiltrative*	*Non-infiltrative*
Superficial	Phlyctenule Catarrhal infiltrate Trachoma pustule Gold hypersensitivity	Vernal ulcer Neurotrophic and exposure ulcer
Deep	Wegener granulomatosis Polyarteritis nodosa† Ulcerative colitis Gonorrhoea‡ Bacillary dysentery Psoriasis† Bacterial and fungal ulcers	Rheumatoid arthritis Lupus erythematosus Diffuse systemic sclerosis Mooren's ulcer§ Chemical burn Erythema multiforme Ocular pemphigoid Radiation Rosacea** Vitamin A deficiency**

*Herpes simplex, varicella-zoster, and vaccinia infections are variable and can exhibit any of the above patterns

†Polyarteritis and psoriasis ulcers can occasionally be non-infiltrative

‡Gonorrhoea and other typically infiltrative diseases can become non-infiltrative after treatment with antibiotics or corticosteroids

§Although Mooren's ulcer typically begins and progresses with mild, grey, corneal infiltration, the cellular response is unimpressive for the degree of ulceration.

**Rosacea and vitamin A deficiency ulcers can be infiltrative, particularly with secondary infection or microbioallergy ence with the procedure for the deep infiltrative group. Additional knowledge and experience are necessary before we shall know the true value, indications, and mechanisms of action of conjunctivectomy.

Summary

We report the rapid healing of several cases of marginal corneal ulceration of various aetiologies after the excision of a 4 to 7 mm strip of adjacent limbal conjunctiva. After conjunctivectomy the remaining conjunctiva was loosely recessed (without sutures). In one case with coexisting scleromalacia, we excised strips of adjacent bulbar conjunctiva with equally good results. Some of the cases had failed to respond to other modes of treatment including topical collagenase inhibitors.

One case responded to peritomy and cryotherapy to the ulcer edges, but we have abandoned this treatment in favour of conjunctival excision.

Limbal conjunctivectomy with recession is presumed to act by eliminating conjunctival sources of collagenase and proteoglycanase.

Addendum

Since this paper was submitted for publication, two additional papers concerning the histopathology and conjunctival proteolytic enzymes of Mooren's ulcer and the use of conjunctival excision as treatment have been published (Brown, S. I. (1975), *Brit. J. Ophthal.*, **59**, 670 and 675).

We thank Alfred Hauersperger, MD, Paul Honan, MD, Kenneth Rudolph, MD, Ralph Stewart, MD, and Dana Troyer, MD, for referral of their patients, and Michael Lashmet, MD, for histopathological work.

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Pterygium and its relationship to the dry eye in the Bantu

LEON GOLDBERG AND ROBERT DAVID
From the Department of Ophthalmology, University of the Witwatersrand, and Baragwanath Hospital, Johannesburg, South Africa

The many diverse theories put forward to explain the pathogenesis of pterygia testify to the fact that their aetiology has as yet not been adequately explained. In recent years ultraviolet irradiation (Cameron, 1962; Elliot, 1966; Peckar, 1972) and microtrauma (Kubik, 1975) have been suggested as being major environmental predisposing factors. One theory is that tear film abnormalities cause local drying of the cornea and conjunctiva which in turn predisposes to these new growths (Barraquer, 1965; Elliot, 1966; Mackie, 1971; Greer, 1972; Paton, 1975). Elliot (1966) stated that the sequence was ultraviolet light causing drying and that this was followed by the pterygium. These theories have been supported by studies of geographical distribution (Cameron, 1962)—pterygia appearing to occur more frequently in hot, dry climates—and by clinical and biochemical studies of the tear film (Mackie, 1971). Our study was undertaken to investigate the correlation between the occurrence of pterygia and the 'dry eye'.

Material and methods

Both the patients with pterygia and the controls were drawn from Bantus living in Johannesburg, South Africa (latitude 26°S), an industrial urban area with more than 250 sunny days a year. This area is within the latitudes 30° N and S where the incidence of pterygia is regarded as being highest (Cameron, 1962).

Forty-three patients with unilateral and eight with bilateral pterygia (59 eyes) and 23 normal subjects (46 eyes) aged between 44 and 79 years of both sexes were studied. The patients presented with one of three complaints: cosmetic, optical, or those due to secondary infection. No age or sex differences were found.

As the 'dry eye' is defined as being either a quantitative or qualitative dysfunction of the tear film (Dohlman, 1971), we submitted all our patients and controls to Schirmer's tests and fluorescein break up time tests. The Schirmer's test was used to determine the quantitative tear formation. 12 mm wetting or more on the 5×30 mm strip of N° 41 Whatman filter paper after five minutes was considered to be normal (Moses, 1970).

The fluorescein break up time test was used to measure the quality of the tear film (Girard and Moore, 1969). A sterile Ayerst fluorescein strip was used and the tear film break up studied using the Cobalt light attachment of the Haag-Streit 900 slit-lamp. An intact tear film after 30 seconds was considered to be normal (Norn, 1969).

These tests were done when there was no clinical evidence of superimposed infection or other irritation which could predispose to excess tearing.

Results

The patients and controls were divided into two groups; those in whom the results of both Schirmer's and fluorescein break up time tests were normal and those in whom either or both tests were abnormal according to the above criteria (Table I).

Of the 59 eyes with pterygia, 19 showed normal tear film and 40 showed some abnormality, whereas in the 46 control eyes 15 were normal and 31 abnormal. These results were analysed statistically and the difference was shown to be of no significance (χ^2 with 1° of freedom = 0; P—not significant).

Twenty of the patients with unilateral pterygia had the results of these investigations on the affected eye compared with those of the fellow eye (Table II). This showed that eight of the eyes with pterygia and nine of the normal eyes had normal tear films. This was again not statistically significant (χ^2 with 1° of freedom = 0; P—not significant).

Discussion

The finding of so many 'abnormal' results in both Schirmer's and fluorescein break up time tests in the trial groups and controls in spite of the fact

Table I *Results of tests for patients and controls*

Test	*Patients*		*Controls*	
Normal, Schirmer's Normal, fluorescein break up time	19		15	
Abnormal, Schirmer's Normal, fluorescein break up time	10		11	
Abnormal, fluorescein break up time Normal, Schirmer's	9	40	7	31
Abnormal, fluorescein break up time Abnormal, Schirmer's	21		13	

Address for reprints: Dr Leon Goldberg, Department of Ophthalmology, University of Witwatersrand, Medical School, Hospital Street, Johannesburg 2001, South Africa

Table II *Patients with unilateral pterygia*

Test	*Eye with pterygium*		*Unaffected eye*	
Normal, Schirmer's Normal, fluorescein break up time	8		9	
Abnormal, Schirmer's Normal, fluorescein break up time	2	12	1	11
Abnormal, fluorescein break up time Normal, Schirmer's	5		3	
Abnormal, fluorescein break up time Abnormal, Schirmer's	5		7	

that in none was there any symptom that could be related to 'dry eye', emphasized the present inadequacy of these gross tests. The Schirmer's test has been described by Wright (1971) as being the 'only practical test of tear flow' but being 'of an unphysiological variety'.

This study has been one of many into the function of tears in the eyes of patients with pterygia. De Ocampo, Valenton, and Chavez (1969) could not show any relationship between the pH of the tears and incidence of pterygium in a population group in the Philippines. Our study using these gross tests, has failed to support the hypothesis of Mackie (1971) and Paton (1975) who support a primary tear film abnormality predisposing to pterygium formation.

If the mechanism of production of pterygia is initiated by ultraviolet light, as suggested by Elliot (1966), it has not been shown to be mediated by its effect on the tear film.

Summary

A comparative study was performed on two groups of Bantus in Johannesburg to see if there was any relationship between the 'dry eye' and pterygia, but no correlation was found.

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Dacryolith formation around an eyelash retained in the lacrimal sac

JEFFREY L. JAY AND WILLIAM R. LEE
From the Tennent Institute of Ophthalmology, University of Glasgow, Glasgow

Chronic dacryocystitis with mucocele of the lacrimal sac is common in cases of epiphora, but the initial factor causing obstruction of the naso-lacrimal duct often remains uncertain and pathological examination of excised lacrimal sac tissue commonly shows a chronic, non-specific inflammatory reaction. On rare occasions a dacryolith has been found within the inflamed sac but most of these dacryoliths have occurred in association with mycotic infection and usually accompany the more common canalicular concretions (Duke-Elder, 1974). Four cases have been reported in which *Candida albicans* infection was considered the initiating factor (Fine and Waring, 1947; Wolter, Stratford, and Hamell, 1956; Wolter and Deitz, 1963), but Jones (1965) failed to find any evidence of yeast-like cells in 25 casts from cases of naso-lacrimal obstruction. In one case of argyrosis reported by Grönvall (1944), a laminated dacryolith had formed round a black central nidus of silver salts; from another patient, Kofler (1941) described a stone with coarse scaly masses at its centre.

It is possible that the initiating factor could be the presence of a lash trapped in the lacrimal sac. The following report describes such a case.

Case report

A 55-year-old man had complained for 10 months of a watering and irritable left eye. The condition began with pain at the inner canthus and there was a profuse yellow discharge. The yellow discharge was only partly controlled by antibiotic drops.

Examination revealed a palpable mucocele of the lacrimal sac and digital compression produced mucopurulent reflux from the puncta. Syringing of the lacrimal passages and macrodacrocystography confirmed the site of obstruction at the lower extremity of a distended sac. The control film showed no evidence of calcification within the lacrimal apparatus and no filling defect was detectable in the contrast medium filling the dilated sac. A mixed growth of coagulase positive staphylococci and diphtheroids was cultured from the discharge.

Dacryocystorhinostomy was performed and when the lacrimal sac was incised, copious mucus spilled out to reveal an elongated yellow dacryolith which was impacted in the upper end of the naso-lacrimal duct. This was submitted to pathological examination together with the excised posterior flaps of the sac wall and nasal mucosa.

The patient had no further symptoms and was discharged from supervision four weeks after the operation.

PATHOLOGICAL FINDINGS

The biopsies of the sac wall showed ulceration of the mucosa and non-specific inflammatory infiltration of the fibrotic wall. The nasal mucosa contained a scattered lymphocytic infiltrate.

The dacryolith was Y-shaped (6 × 1 mm) and the surface was nodular (Fig. 1). Microscopical examination revealed a hair in the centre of one limb of the Y-shaped structure which was otherwise composed of layers of basophilic granular and eosinophilic homogeneous material interposed with layers of polymorphonuclear leucocytes and lymphocytes (Fig. 2). In Gram-stained sections bacteria were seen as Gram-positive cocci (1 μm diameter) in chains (Fig. 2 insert). An additional feature was the presence of yeast-like structures (2–4 μm diameter) which stained with periodic acid-Schiff stain and had a clear capsule (Fig. 3). The alizarin and von Kossa stains for calcium were equivocal although the appearance of the basophilic granular material in the matrix was suggestive of dystrophic calcification.

In an attempt to clarify the structure of the dacryolith

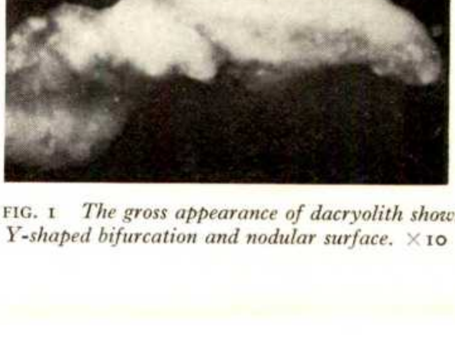


FIG. 1 *The gross appearance of dacryolith showing Y-shaped bifurcation and nodular surface.* × 10

Address for reprints: J. L. Jay, Tennent Institute of Ophthalmology, Western Infirmary, 38 Church Street, Glasgow G11 6NT

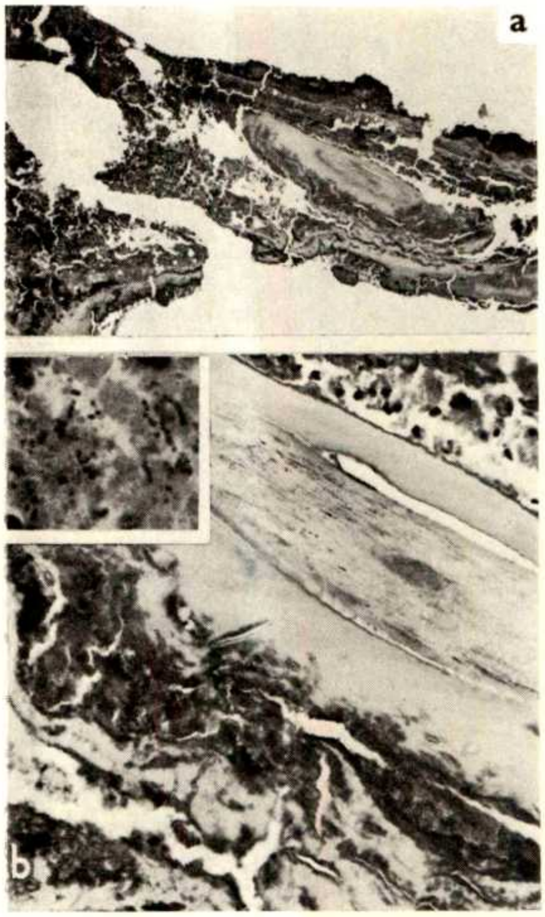


FIG. 2 (a) *A low power view of dacryolith showing the hair in centre of specimen. Haematoxylin and eosin.* ×40. (b) *A higher power showing edge of the hair, lamination of hyaline material and inflammatory cells. Haematoxylin and eosin.* ×250. *Insert shows cocci in granular debris. Gram.* ×1000

further, the remainder of the tissue was removed from the paraffin block and processed for electron microscopy, using the technique described by Jensen (1974).

In the tissue available for study, lymphocytes and polymorphonuclear leucocytes were identified, but many of these cells were degenerate and in some areas there were circular bodies of vesicular and granular nature which could have been derived from cell breakdown (Fig. 4). Elsewhere the ground substance was amorphous but was lined by a zone of granular electron-dense material. Hydroxyapatite crystals were not identified in the electron-dense zones (Figs 4 and 5).

The yeast cells were surrounded by an electron-lucent zone which was probably a retraction artefact because elements of the capsule could be identified in these spaces. The cell wall was thin (approximately 5 mm) and the cell membrane was invaginated. The detail of the cytoplasmic organelles and nuclei was lost although occasional mitochondria could be identified. The dimensions of these organisms were similar to those described for *Candida* sp. (see Carbonell, 1971). Bacterial forms were not present in this region of the material.

Discussion

In patients who complain of conjunctival irritation it is not uncommon to find an eyelash within one

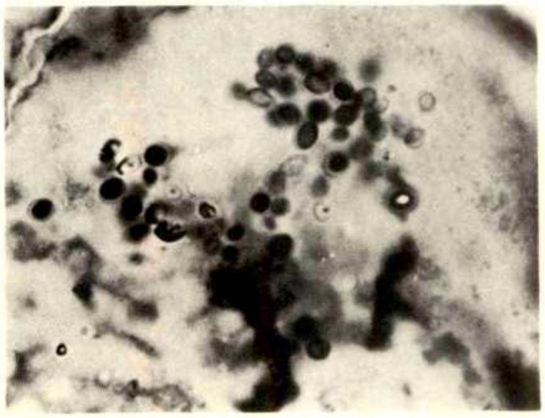


FIG. 3 *Yeast-like organism surrounded by hyaline material. Note the clear capsule. Periodic acid-Schiff.* ×1000

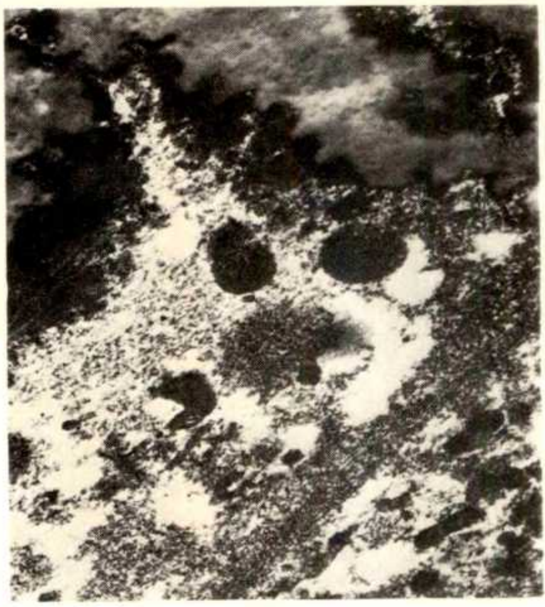


FIG. 4 *Electron micrograph showing amorphous material with electron-dense border. Ground substance (below) has granular and fibrillar consistency and contains round bodies which are probably cellular breakdown products.* ×30 000

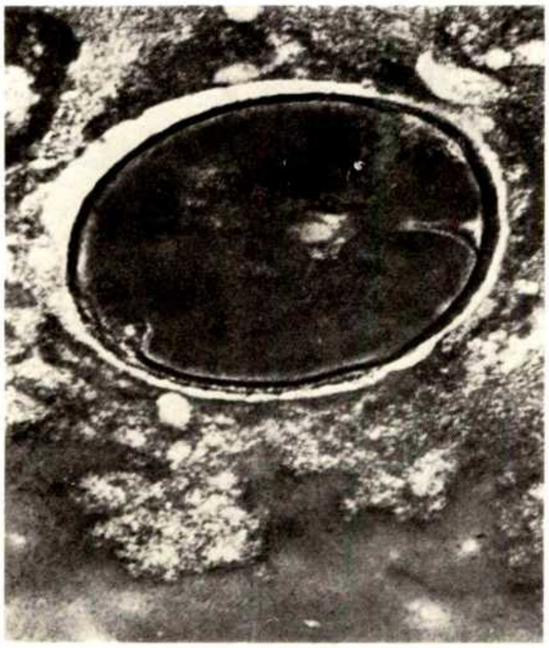
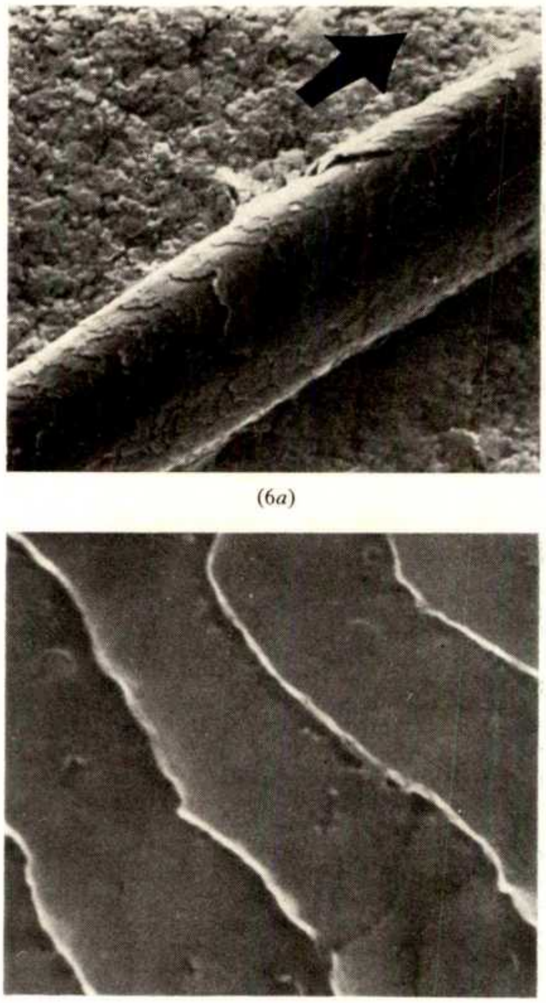


FIG. 5 *Electron micrograph of a yeast within fibrillar and granular ground substance, amorphous component of the ground substance is shown below.* ×35 000

of the lacrimal canaliculi. The end of the lash projects from the punctum and rubs on the adjacent bulbar conjunctiva. We have seen two examples of this type of conjunctival irritation and Boase (1949) reported a similar case with a localized granulomatous reaction in the conjunctiva. Cilia have been found very rarely in the lacrimal sac although it is possible that they may either be destroyed by an acute inflammatory reaction within the sac or continue downwards and escape into the nose. Some support for the latter hypothesis is produced by Gundersen (1942) who described a cast containing a cilium which had been blown out of the nose in a case of naso-lacrimal obstruction. One of the casts described by Jones (1965) also contained a lash.

The histological examination of the dacryolith provided similar information to that previously described (Duke-Elder, 1974). There is general agreement that a foreign body, in association with secondary inflammation, acts as a nidus for deposition of various types of material—for example, fibrin, cellular breakdown products, bacteria, fungi, and mucoprotein substances—and it is assumed that the last acts as a ground substance for calcium deposition. The ultrastructural variations in the matrix support the concept that there is wide chemical variation in the layers of the dacryolith. Although precise chemical identification is not possible with electron microscopy, it is a valid technique for the demonstration of hydroxyapatite crystals which are participating in dystrophic calcification. It is therefore of interest that hydroxyapatite was not identified in the material studied, so that if calcification were occurring it was unlikely to be by the mechanisms association with cell mediated calcification (Anderson and Reynolds, 1973).

The demonstration that the *Candida* sp. organisms were confined to a localized zone of the dacryolith suggests that the fungal infection



(6*a*)

(6*b*)

FIG. 6 *Scanning electron micrographs of surface of a human eyelash.* (a) *Low power view of hair shaft.* ×600. (b) *A higher magnification to show the stepped ridges which impart preferential movement in direction of arrow.* ×3000

occurred at a specific time in the evolution of the dacryolith.

It is interesting to speculate how a pliable lash is able to enter the punctum and pass onwards into the canaliculus. Stern (1952) noted that a lash is thicker than the narrowest part of the canaliculus and he suggested that the lash might be sucked along the canaliculus.

It seems more likely that the movement in the canaliculus is the result of the surface features of the hair itself. The surface structure of a human eyelash can easily be demonstrated by scanning electron microscopy (Fig. 6). The illustration shows an imbricated surface resembling the overlapping scales on a fish. This dictates a preferential direction of movement towards the root end of the lash as indicated by the arrow in Fig. 6. A simple demonstration may be performed by placing a hair between the two index fingers and rubbing gently to and fro along the length of the hair. It will always move towards its root. Although most reports of eyelashes found in the lacrimal canaliculi do not specify which end of the lash had entered first, the root was leading in the cases seen by the authors and those described by Stern (1952) and illustrated by Werb (1971).

Summary

A dacryolith was discovered in the lacrimal sac during a dacryocystorhinostomy for chronic dacryocystitis in which there was mucocele formation. Morphological examination confirmed the presence of an eyelash at the centre of the stone and electron microscopy demonstrated the presence of fungi (*Candida* sp.) in a matrix which was of markedly variable morphology.

The mechanism by which a hair enters the punctum and passes along the canaliculus may be attributed to the step-like pattern of ridges on the surface of a hair. The directional nature of these ridges dictates preferential movement towards the root end of the hair and prevents movement in the opposite direction.

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Plastic surgery on the upper eye-lid after enucleation of the eye

OTTO RIEBEL
From the Department of Ophthalmology, Medical Faculty Hospital, University JEP Brno, Czechoslovakia

The removal of an eye not only means loss of sight to the patient, but it produces a cosmetic blemish.

The principal cosmetic imperfections are:

1. Restricted movement of the prosthesis.
2. An obvious deep groove in the upper eye-lid.

Restriction of movement of the prosthesis can be partially overcome by the use of various types of implant (Hughes, 1948; Jendralski, 1941; Knobloch, 1940; Vanýsek, 1951).

Treatment of the deep groove in the upper lid which is a constant operative result of enucleation in the absence of a buried implant, is the subject of this clinical note.

Operation procedure

The basis of the operation is to separate the middle third of the tendon of the upper lid levator from the tarsal plate and stitch this prepared strip to the periosteum of the upper edge of the orbit (Fig. 1). The aim of the operation is the return of the tarsal plate and the upper lid to its preoperative position (Figs 2 and 3).

Address for reprints: Professor MUDr. Otto Riebel, Head of Department of Ophthalmology, Medical Faculty Hospital, University JEP, Brno, Czechoslovakia

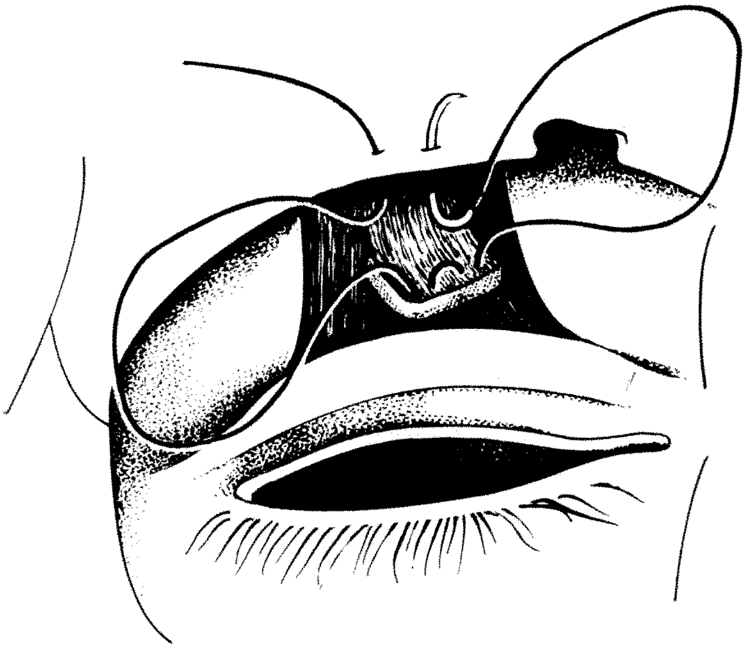

FIG. 1 *After exposing the tendon of the upper lid levator a stitch is put into the middle third of the tendon. This part of the muscle is clipped away from the tarsal plate and with help of lengthwise incisions a muscle lobe is created and fixed to the periosteum of the orbital edge*

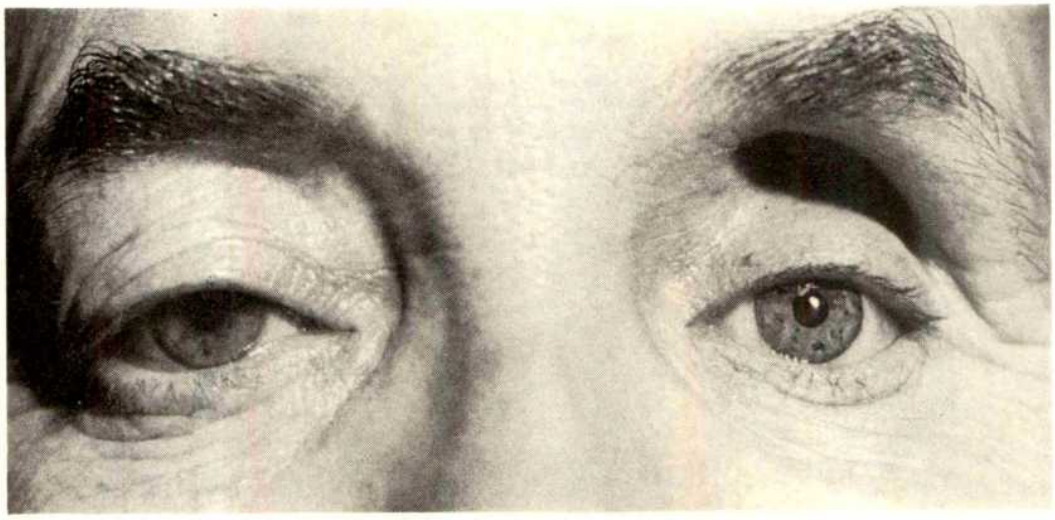

FIG. 2 *The preoperative state: deep groove of the upper lid after enucleation of left eye*

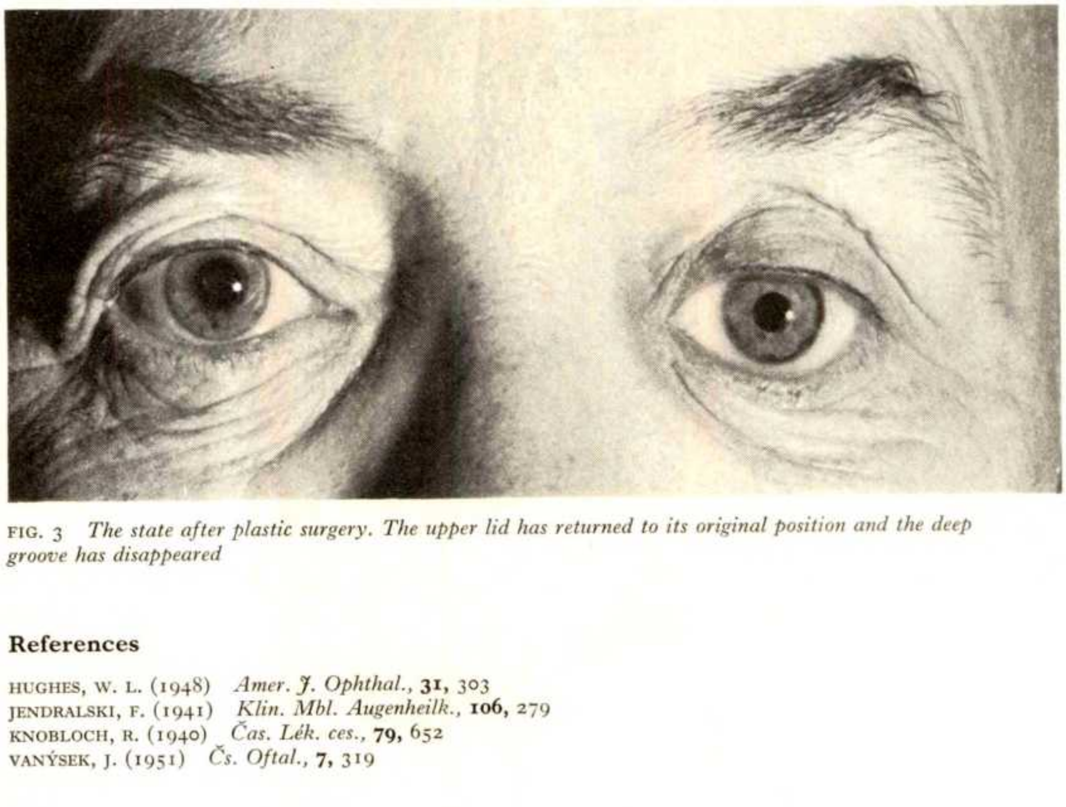

FIG. 3 *The state after plastic surgery. The upper lid has returned to its original position and the deep groove has disappeared*

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Book reviews

Immunopathology of the Eye. By A. H. S. Rahi and A. Garner. 1976. Pp. 343, figs, tables, refs. Blackwell, Oxford (£11·50)

The emergence of the vertebrate phyla has been accompanied by the evolution of an elaborate system for the recognition and elimination of both invading pathogens and abnormal mutant cells. Phylogenetic studies indicate that the ability to mount a specific immune response to potentially harmful agents is correlated with the presence of lymphoid tissue. The central role in this protective mechanism is the lymphocyte, regarded until quite recently, as a phlegmatic spectator. Herein lies the main theme of *Immunopathology of the Eye.*

The authors have described step-by-step the rewarding paths of research which were followed in the recognition of this highly complex and subtle mechanism. The existence of two distinct populations of lymphocytes, the nature of antigens, the structure and specificity of antibodies, the types of hypersensitivity and the concept of tolerance to the body's own tissues are all clearly described and their individual influence is discussed.

The eye has a unique place in immunology by virtue of its two avascular structures, the cornea and the lens, which are almost isolated from this system. The vascular uvea and the conjunctiva, however, provide centres for lymphoid reaction. Furthermore the absence of lymphatic drainage in ocular tissues amounts to a loss of the afferent limb of the immune response. Ocular antigens have no alternative but to drain into the blood stream and thus diluted may fail to stimulate any lymphoid reaction or alternatively, if their concentration is high enough, evoke a generalized response.

Applying these fundamental concepts to the various ocular structures, chapters follow on the conjunctiva and eyelids, the cornea, the uvea, lens, retina, optic nerve, and orbit. The immunology of ocular tumours has deservedly a section of its own and the chapter on ocular involvement in systemic disorders leads us towards an understanding of the aetiology of a group of diseases which have baffled the greatest medical minds since the beginning of time. A final chapter on the mode of action of some of the immunosuppressive agents brings to a close an absorbing account of ocular immunopathology.

The authors are to be congratulated on summarizing present knowledge of this difficult and expanding subject in such a way as to make it understandable to the clinician and investigator alike. Apart from its undoubted practical and scientific value their survey cannot fail to recall in the reader that sense of wonder which all students of medicine have experienced at some stage in their career and perhaps have lost awhile.

S. J. H. MILLER

Neuro-ophthalmology. By R. Sachsenweger. 1975. Pp. 627, 332 figs, 32 tables, refs. Thieme, Leipzig (DM107)

This book compares unfavourably with most English language texts on the subject. It contains no references (only a list of monographs at the end) so it must be considered purely as a textbook, and as such it is a formidable introduction to a complex subject. On the credit side the specialty has been fully covered by the 36 contributors with the exception of investigative procedures where the role of fluorescein angiography is understressed and no mention is made of the recent important advance in neuroradiological techniques with the introduction of the EMI scanner. The section on neuroanatomy is excellent and the text is adequately, although not profusely, illustrated in monochrome.

R. COAKES

Symposium on Glaucoma. By O. M. Ferrer. Pp. 260, figs, tables, refs. Thomas, Springfield, Illinois ($22·50)

As one glaucoma symposium follows another the question must arise as to whether their frequency is justified by the rate at which new information about glaucoma is being accumulated. But perhaps these symposia have functions other than the communication of the latest research work; perhaps they provide a milieu for sober reflection on the significance of new findings when the first flush of optimism has faded and the time is right for the real value of these new findings to be communicated to those who have the task of looking after patients with glaucoma. Such is the impression gained from reading the account of the proceedings of the sixth meeting of the Horacio Ferrer Eye Institute held in Miami in March 1973. Compared with some other symposia there is relatively little about the physiology of the intraocular pressure and most of the material is presented in terms of its practical application, the main topics covered being the optic disc and the importance of its assessment in the diagnosis and management of glaucoma, medical treatment, and surgery. A quick way to learn most of the important points which were raised is to read the 10 pages of the preface. On the technical side of the publication, it is a pity that the quality of the paper is not matched by the typographical standard because there are several spelling mistakes and similar errors. It does not take long to read this book and it is time well spent if one is looking for good commonsense ideas about glaucoma in clinical practice.

J. GLOSTER

The Wilmer Ophthalmological Institute: The First Fifty Years, 1925–1975. By M. E. Randolph and R. B. Welch. 1976. Pp. 216, 78 figs. Williams and Wilkins, Baltimore ($12)

A golden commemoration is, and has long been, an occasion for congratulation, and when the anniversary concerns the Wilmer Ophthalmological Institute in Baltimore, opened in 1925—22 years before our Institute in London—to the congratulation must be added rejoicing in view of the immense value its influence has had on the development of ophthalmology in America and elsewhere.

The story of its birth is interesting. Like most golden events it was all due to a woman. Mrs Aida Breckinridge was one of those typically American women—handsome, intelligent, and immensely determined. Fortunately for Johns Hopkins she developed glaucoma; more fortunately her surgeon was Wilmer; most fortunately the operation was a success. She considered that Wilmer deserved a better milieu than was afforded by the Episcopal Eye, Ear, and Throat Hospital in Washington, although he had the largest and most distinguished private practice in America. Mrs Breckinridge's views can clearly be understood for Wilmer was the handsomest man the reviewer has seen and one of the most charming and, withall, an excellent ophthalmologist and surgeon. So with the utmost zeal and determination, with the help of the Rockefeller Foundation and Johns Hopkins Hospital, she collected $3 700 000 and the Wilmer Institute was born.

This book divides the history of the first 50 years of the Wilmer Institute into three eras, the periods of its three directors and professors: The Wilmer era 1925–34, the Woods era 1934–55, and the Maumenee era 1955–75. At first the Institute took over a somewhat rundown building in the hospital complex until a new building was completed in 1929, and before Wilmer retired subdepartments of pathology, physiology, bacteriology, chemistry, and physiological optics had been established and the Institute had become recognized as one of the leading centres in ophthalmology. Woods's directorship saw further growth and expansion and a great enhancement of its reputation, partly due to the unique achievements in research of Alan Woods himself and the amazingly comprehensive original and classical work of Jonas Friedenwald. When on the retirement of Woods, Edward Maumenee, an old Johns Hopkins student, was enticed from the chair at Stanford University to return to the Institute its work and influence steadily increased, despite the premature and lamented death of Friedenwald. During his tenure, in 1964, the Woods Research Building and the Friedenwald Library greatly increased the capacity of the institution together with the renovation of the whole building.

This book gives these events in a fascinating and detailed way. It tells how ophthalmology evolved during those 50 years, the changes in cataract and retinal and vitreous surgery, the rise and decline of Woods's belief that tuberculosis was the cause of uveitis and in its treatment by the use of 'barrels of tuberculin' and later of streptococcal vaccine, and the host of medical and technological advances that have characterized these years, particularly in Maumenee's time.

The book has also great personal interest. There are full biographies of the three directors, of Jonas Friedenwald, Frank Walsh, Charles Iliff, Louis Sloan—and the artist, Annette Burgess. Not the least feature of interest is the record, with photographs, of the house-staffs during these years; it is extraordinary how many of them have disseminated into responsible posts all over the United States, and how different they look now compared with their appearance in their youth.

In this volume we almost have a history of American ophthalmology over half a century. For indeed the Wilmer Institute has been fortunate—in the ability of its directors, in the great mass of medical clinical material available to it in Johns Hopkins Hospital, and in the availability of superb laboratories for the basic sciences in the associated university.

STEWART DUKE-ELDER

Notes

The Page and William Black Postgraduate School of Medicine

New York, 22 January 1977

A postgraduate course on 'Dyslexia: current developments', co-sponsored by the New York State Branch of the Orton Society Inc. under the direction of Virginia Lubkin, MD, FACS, will be held at the Mount Sinai Medical Center.

Further information may be obtained from the Director, The Page and William Black Postgraduate School of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, NY 10029, USA.

Seventeenth Annual Instructional Course in Contact Lens Fitting

New Orleans, 17–19 February 1977

The Rudolph Ellender Medical Foundation (an AMA-approved course in continuing medical education) will be presenting its seventeenth annual instructional course. Special convention room rates will be offered by the Fairmont Hotel.

Further information may be obtained from Jos. A. Baldone, MD, President, Rudolph Ellender Medical Foundation Inc. Roof, Delta Towers, New Orleans, 70112, USA.

Obituary

Edmund B. Spaeth, MD, 1890–1976

Edmund Benjamin Spaeth died on 18 August at the age of 86 in the Chestnut Hill Hospital, Philadelphia, after a short illness.

Mr Keith Lyle writes: Many of us will remember Ned (as he was known to his friends) as a frequent visitor to this country, usually in the summer when he often attended the Oxford Ophthalmological Congress. He and his wife Lea were delightful companions at any gathering and made friends with everyone they met. For several successive years at Oxford it was traditional for some of their old friends to join them on the first night of the congress for a private dinner party at the Randolph Hotel where their favourite meal was a mixed grill followed by strawberries and cream—sometimes they were hosts and sometimes some of us were. These evenings were always great fun but when Ned felt it was time for bed he would diplomatically get up from his chair and say, 'Well folks it has been grand to see you all again'. This was a signal for the party to break up.

He gave several papers at Oxford which were always interesting and well presented. He kept closely to his text and rarely exceeded the time allotted to him.

I think he was at his best when doing a difficult operation in his home surroundings at the Wills Eye Hospital. I well remember in the 1950s arriving on a Saturday afternoon at Philadelphia on my way to Washington, and calling at the hospital to see if Ned was around. To my joy he was just about to start removing an orbital tumour. He invited me to watch. It was a specially interesting case and he was having the operation filmed. Not only was his surgical expertise a pleasure to behold but he had the capacity to demand a high standard of efficiency from his two assistant surgeons and the entire theatre staff. His enthusiasm was quite infectious. There was never a dull moment during the operation which took 1 hour and 50 minutes.

Edmund Benjamin Spaeth was born in Webster New York on 22 April 1890. His father was a Lutheran Minister and had intended his son Edmund to follow in his footsteps, but the boy declined to do so and at the age of 14 went to work so as to pay for his board and lodging at home.

His medical studies were conducted at the University of Buffalo where he obtained his MD in 1916. He was an intern at the Arnot-Ogden Memorial Hospital Elmira, New York, in 1916–17, and then served in the US Army Medical Corps from 1917 to 1926 where he rose to the rank of major.

In 1927 he took up the practice of ophthalmology in Philadelphia, subsequently holding the post of Professor of Ophthalmology of the Graduate School of Medicine at the University of Pennsylvania 1934–55, and later Professor Emeritus. He was also Vice-Dean of Ophthalmology 1934–55 and Chairman of the Department of Ophthalmology 1943–55. He was consulting ophthalmologist at the US Naval Hospital and at the Graduate Hospital of the University of Pennsylvania, and consulting surgeon at the Wills Eye Hospital, Philadelphia. He gained many medical awards including the Ophthalmic Medal of the University of Buffalo and also the Lucian Howe medal in 1927. In 1966 he received the Ophthalmology Alumni Award in honour of being the first Chief of Ophthalmology at the Walter Reed General Hospital, 1924–26.

He took great interest in plastic surgery and was a founder member of the American Board of Plastic Surgery in 1939. He was also a Fellow of the American College of Surgeons, of the American Academy of Ophthalmology and Otolaryngology, of the Philadelphia College of Physicians, and the Pennsylvania Neurological Society. He was author of *Ophthalmic Plastic Surgery* and of the *Principles and Practice of Ophthalmic Surgery*.

He is survived by his wife and four sons, one of whom, George, is an ophthalmologist; 11 grandchildren and two great grandchildren, and also a sister. Apart from ophthalmology he was devoted to music and a regular attender of the Bayreuth and other musical festivals.

Ned's life was characterized by enthusiasm, fearlessness, honesty, and a capacity for hard work. What he accomplished he did by his own efforts. As a father he was always fair if sometimes a little stern, but he was very proud of the achievements of his children. Ned and Lea were a truly devoted pair and their life was a splendid example to others.

Erratum

CHERRY, P. M. H., and GARNER, A. (1976) Corneal neovascularization treated with argon laser. *Brit. J. Ophthal.*, **60**, 467
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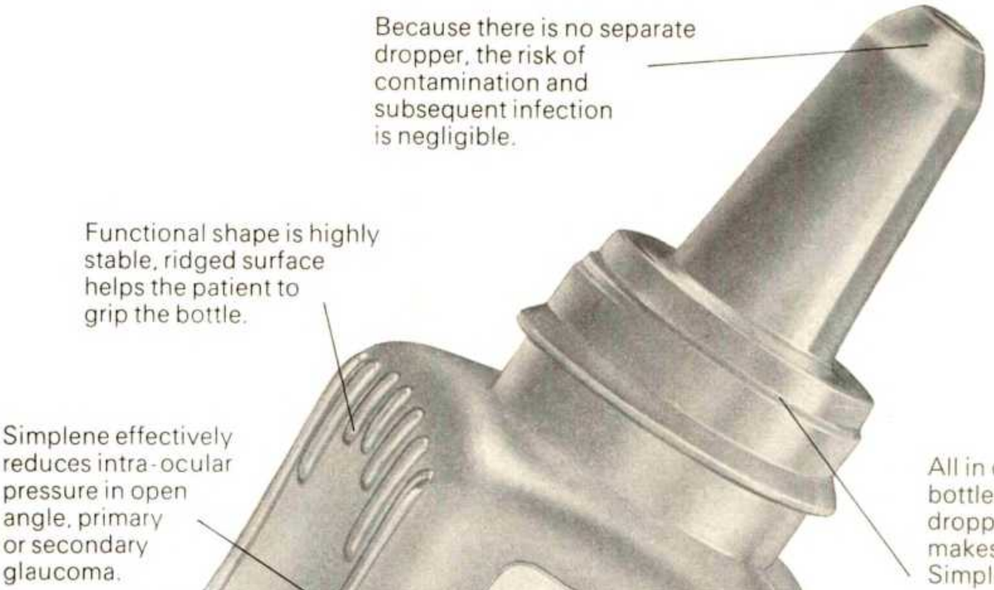

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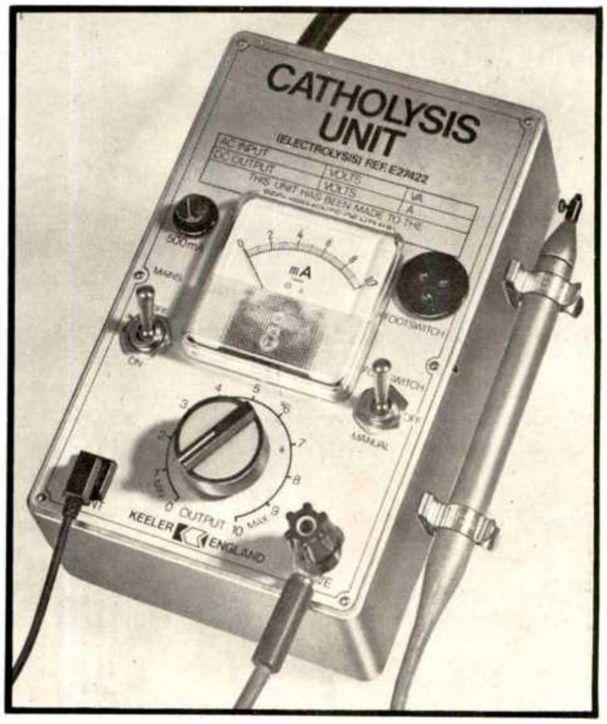

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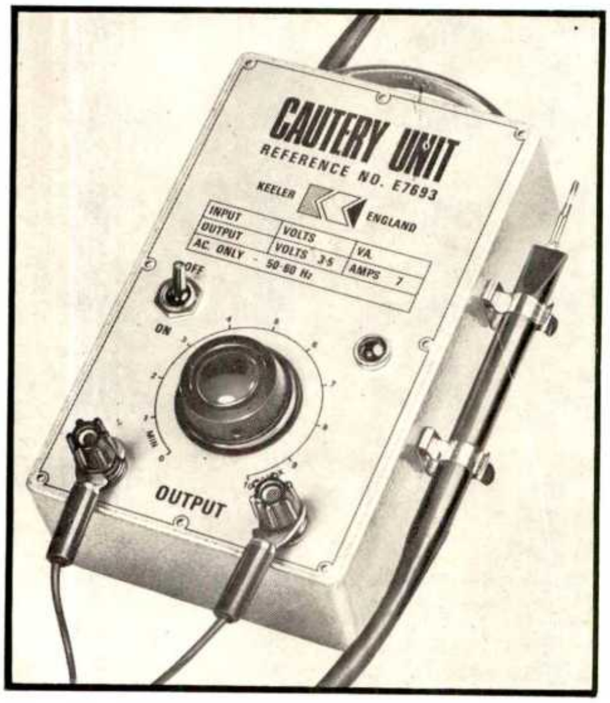

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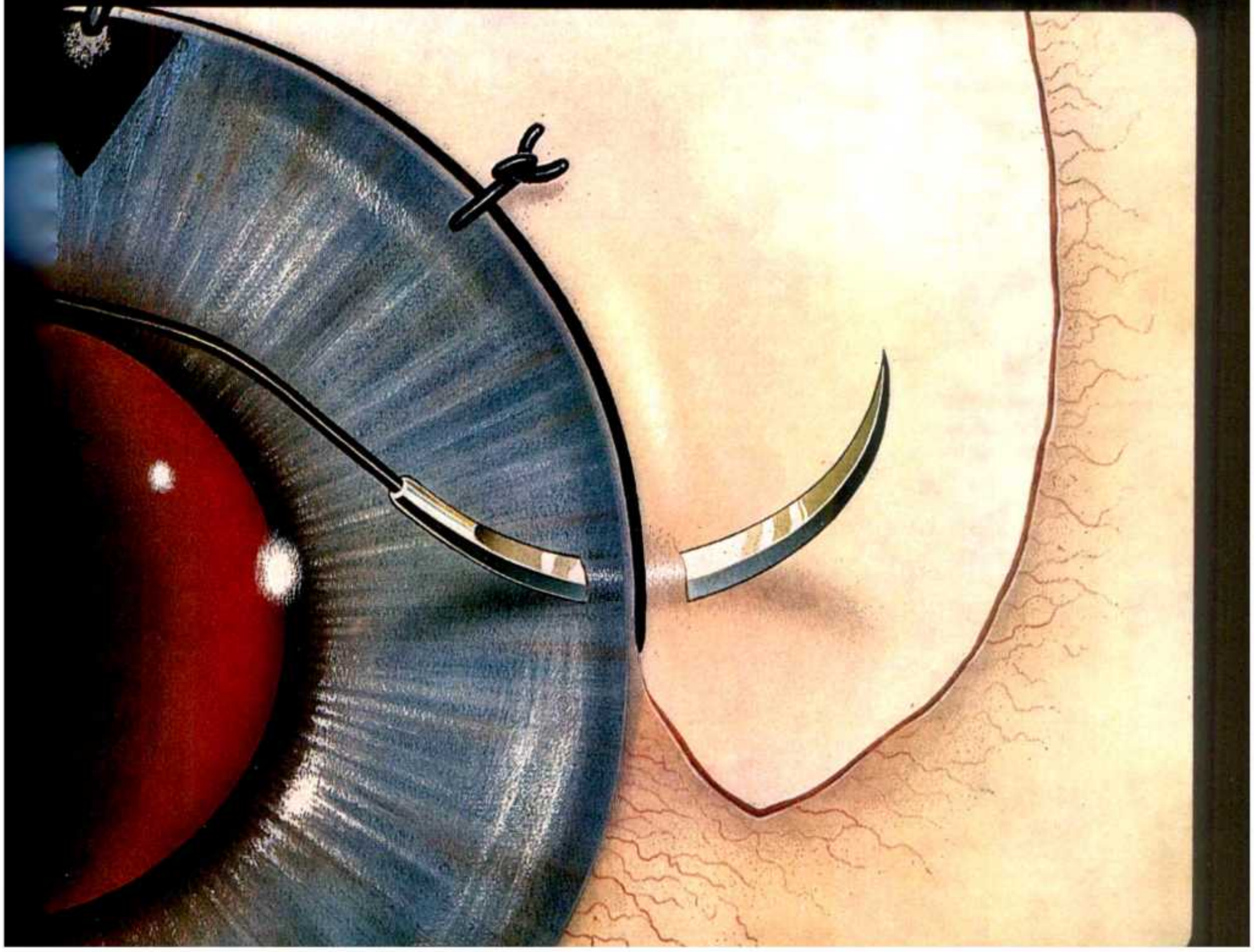

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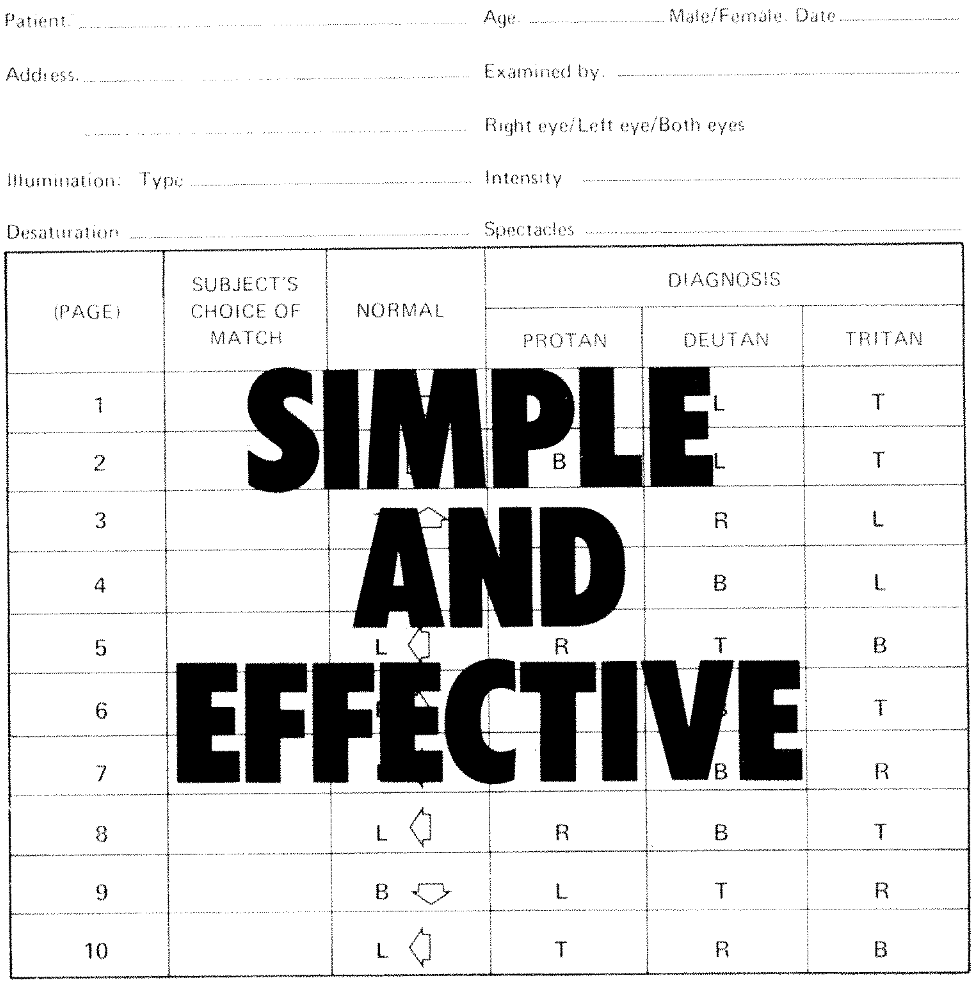

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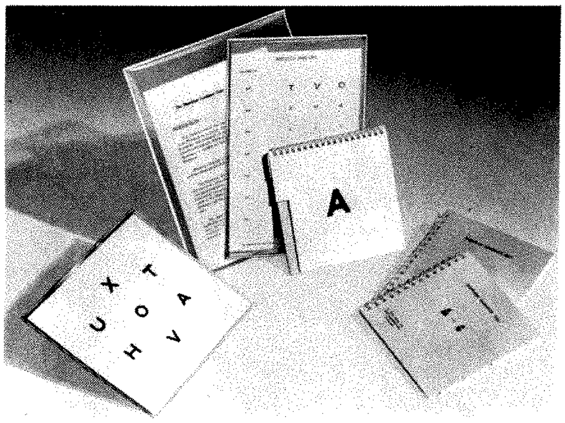

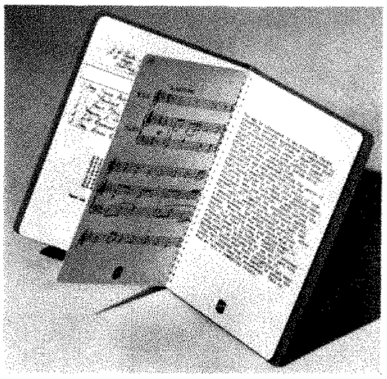

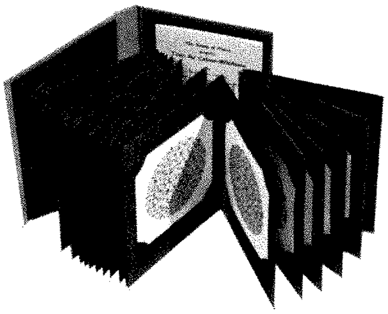

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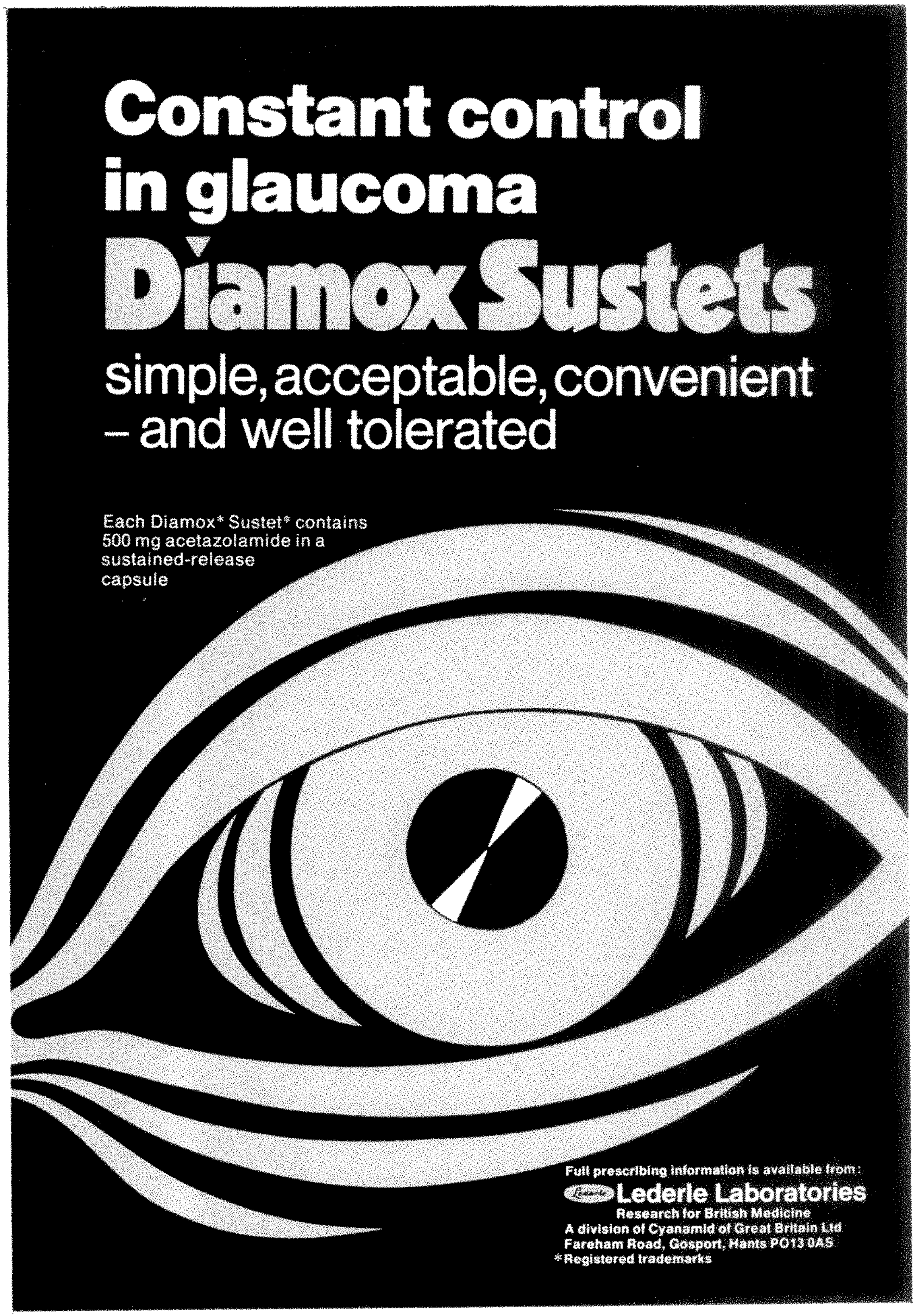

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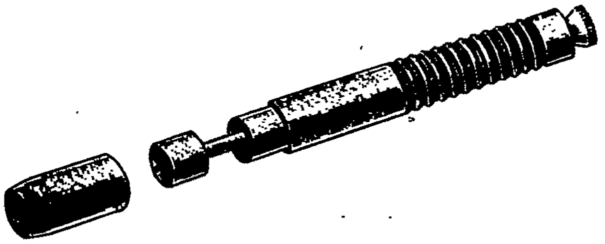

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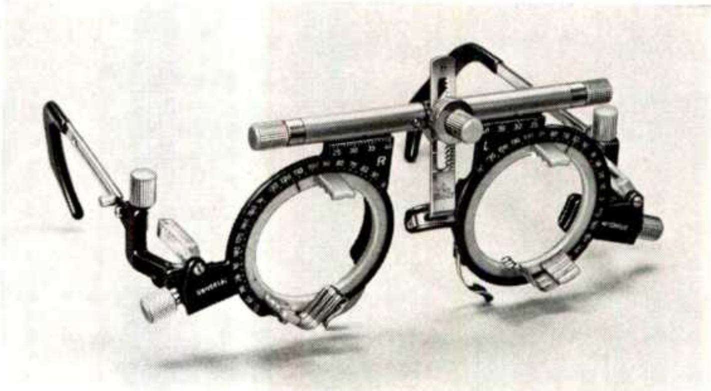

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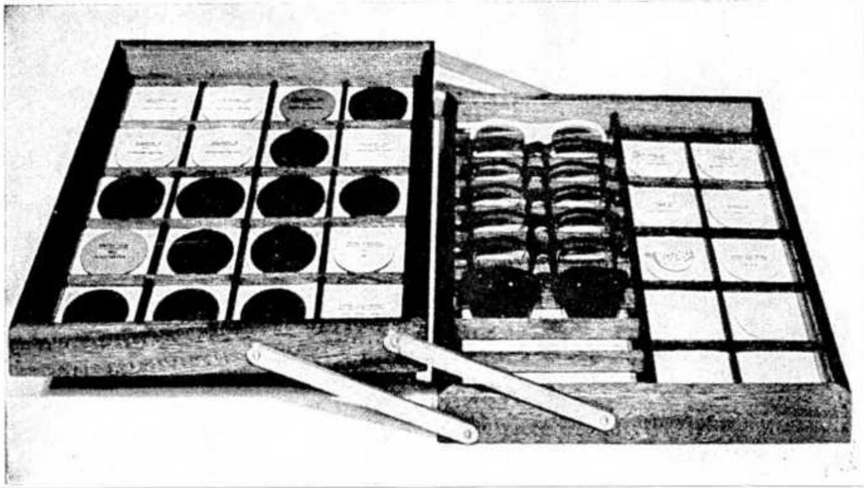

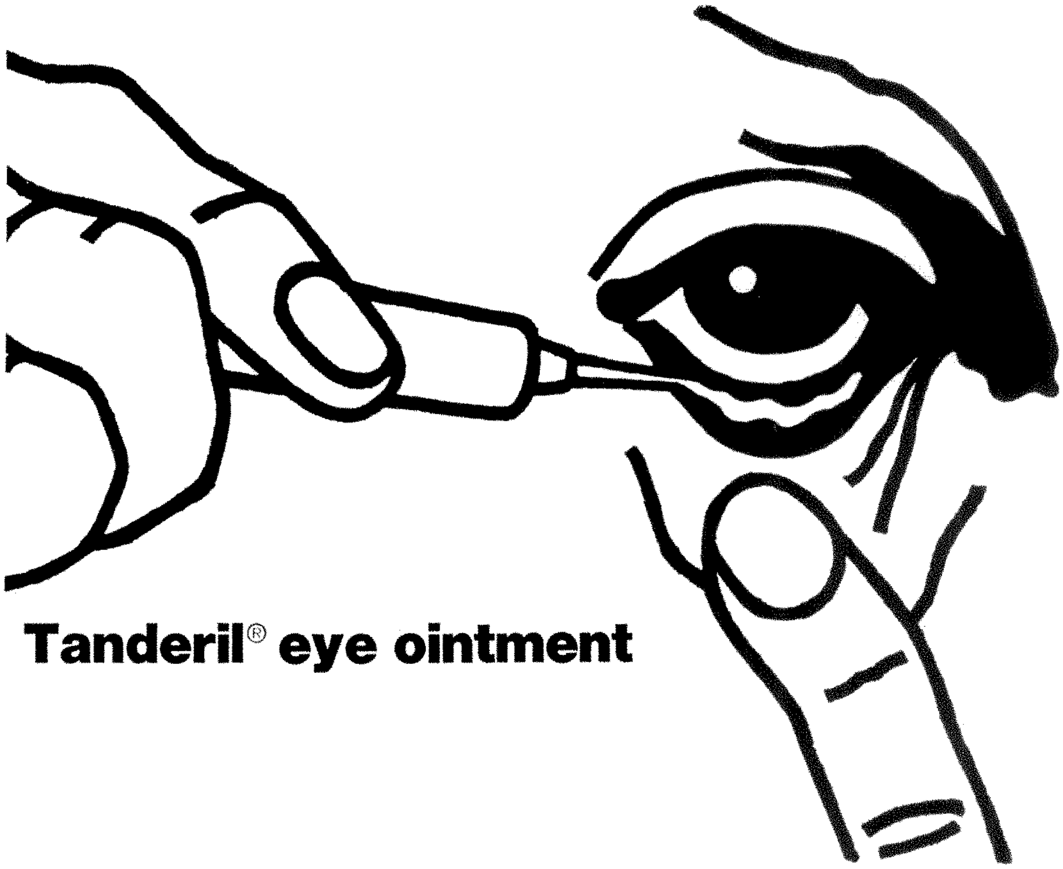

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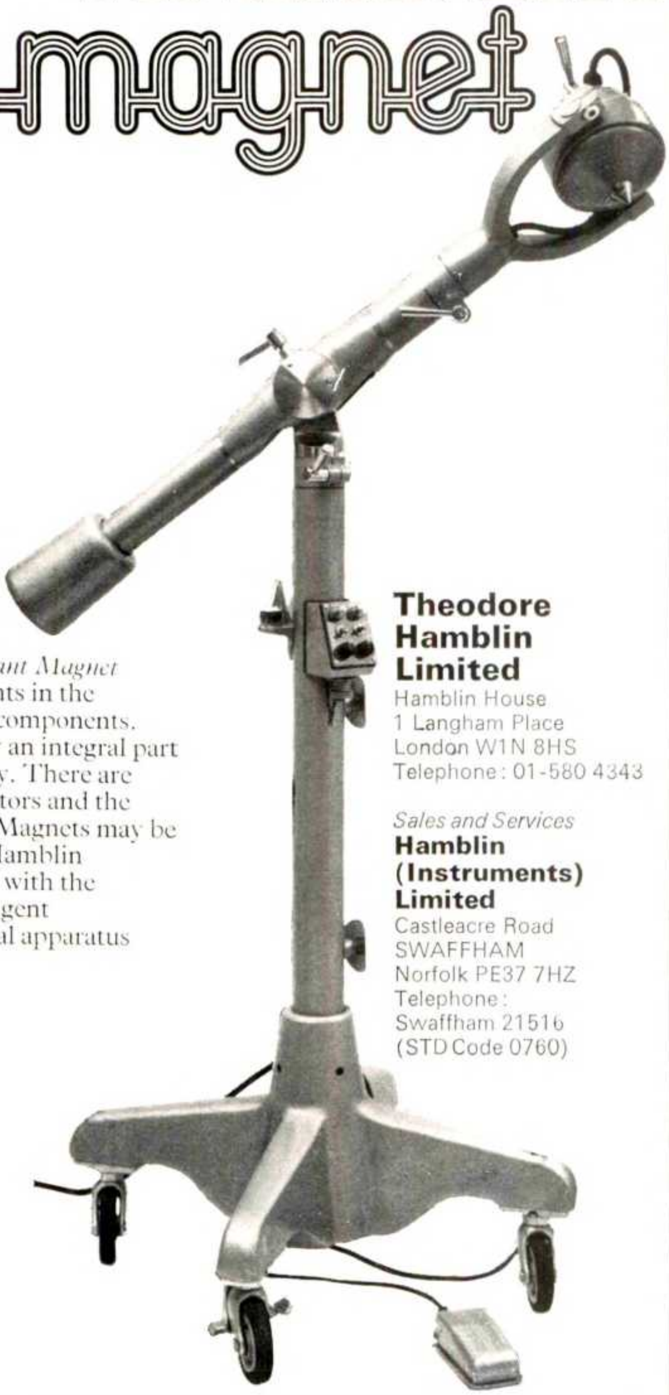

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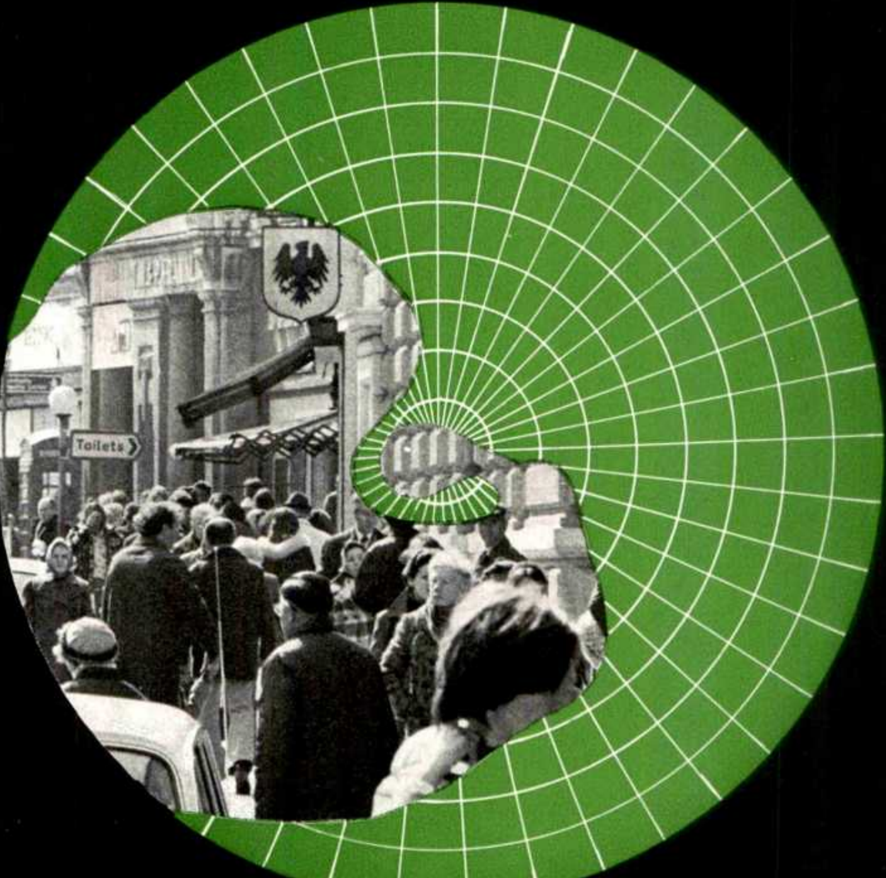

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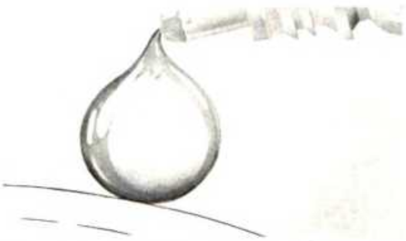

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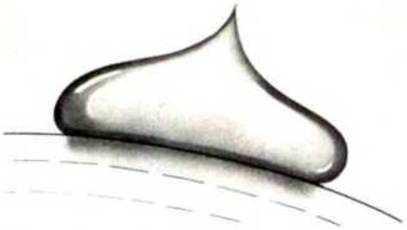

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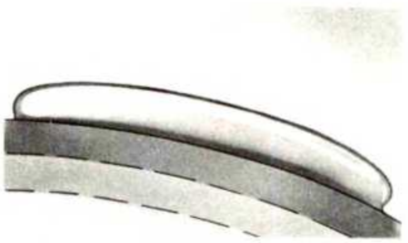

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Brit. J. Ophthal. (1976) **60,** 731

Editorial: Progress in surgical management of ocular trauma

The availability of new methods of treatment and the development of new instruments has had the effect of a fairly rapid evolution in the treatment of perforating injuries to the eye, leading to an obvious improvement in results.

No longer is the retention of a safe eye a satisfactory criterion of success; we must now aim also at a return to normal function.

The trends have been largely predictable. The most important has been the control of infection which in the past not only led to a rapid destruction of the eye but also precluded any primary surgery other than an immediate repair and closure of the wound often after the sacrifice of parts of the uvea and other intraocular contents.

It is difficult to imagine that it was sometimes only possible to cover a leaking corneal wound with a conjunctival flap because surgical facility was less available and suture materials were too coarse for accurate repair.

The introduction of the operating microscope into ophthalmology and the finer instruments and materials which followed led to a more accurate control of wound closure and easier reconstruction of the normal anatomy of the eye.

Re-formation of the anterior chamber with air helped to improve results but the re-formation of the chamber with a physiological solution reflected a more accurate wound closure—watertight instead of airtight.

Not long ago any iris which was prolapsed would be excised; a few surgeons were tempted to replace iris which appeared undamaged in a fresh perforation just as they would try to replace an iris prolapse which occurred after intraocular surgery. The result of this action was unexpectedly good; the eye with replaced iris was often quiet more quickly than a similar eye in which iris had been abcised. Not only that but the eye would have the advantage of a normally acting iris diaphragm and a more normal cosmetic appearance.

Repair of a torn iris diaphragm is being performed more widely and is likely to become the common practice when surgeons are convinced of the safety of iris suturing. The re-formation of the iris diaphragm helps to prevent anterior synechia of the iris to the wound or the angle.

Thus the last few years have seen the development of more complex reconstruction and more comprehensive primary surgery. Many eyes which would have been lost can now be seen to recover not only potential function but also a true return to binocular vision.

Further progress is to be expected in the management of traumatic cataract. It is possible to go further in primary surgery than simply removing swollen lens matter. Instruments with controlled infusion and aspiration coupled with cutting devices and ultrasound emulsification make it possible to remove the whole of the lens cortex with a chosen portion of the lens capsule. If damage involves the vitreous as well then a partial vitrectomy can prevent the rather serious complications of coexistent lens and vitreous damage. There is a suggestion that in cases of early infection and when inflammatory membranes are beginning to form, the radical approach can be extended to the removal of infective and inflammatory foci with improved results.

Some of the fields of advance are still controversial. The use of an intraocular lens to replace a traumatic cataract is advocated by some and condemned by others. There can be no doubt, however, that if a safe intraocular lens is available then its use in such cases permits a closer approach to normal function than by any other means.

These comments are related to the advances in the treatment of perforating wounds of the eye. The prognosis in blunt injury has also benefited from better appreciation of the pathology of vitreoretinal adhesions and the risks of retinal detachment. Progress in the treatment of burns has shown the need for early protection and deferred reconstruction.

Trauma is not the most prevalent cause of blindness in the world but it is certainly the commonest cause of unilateral loss of vision and it affects all countries. It has been justifiably included among the major projects in this Prevention of Blindness Year of the World Health Organization.

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Perforating injuries of the eye

ELIZABETH M. EAGLING
From the Birmingham and Midland Eye Hospital

This review was undertaken to evaluate the outcome of the current management of perforating eye injuries in order to determine reasons for failure to achieve a satisfactory result, and to see where further improvement may be possible.

Since the advent of microsurgical techniques, better wound closure and re-formation of the anterior chamber have led to a greatly improved prognosis for perforating eye injuries (Roper-Hall, 1959). Attention has subsequently been directed towards the management of intraocular damage: the safety of repositing an iris prolapse with an improved visual and cosmetic result has been reported by Callaghan (1956) and by Stein (1958), while immediate aspiration of a damaged lens was recommended (Roper-Hall, 1959) to reduce subsequent intraocular inflammation. More recently, Coles and Haik (1972) stressed the importance of performing an extensive anterior vitrectomy in badly injured eyes to limit the development of intraocular fibrosis leading to phthisis and retinal detachment.

In this present study, 228 patients with perforating eye injuries (nine bilateral) have been reviewed; all were admitted to the Birmingham and Midland Eye Hospital between 1971 and 1974. This study does not include patients with small intraocular foreign bodies and a sealed entry wound, as these constitute a different clinical problem.

Since the complications of perforating eye injuries are now determined largely by the extent of intraocular damage, a simple classification on this basis was adopted. Injuries were divided into four groups as follows: Grades 1 and 2 were injuries confined to the anterior segment; lacerations of the cornea or anterior sclera, with or without uveal prolapse, were classified as Grade 1, but if lens damage was also present, they were classified as Grade 2. Injuries involving the posterior segment with vitreous loss were classified as Grade 3, while the more extensive injuries involving both anterior and posterior segments—that is, both lens damage and vitreous loss—were classified as Grade 4.

This paper is concerned with the outcome of the injuries confined to the anterior segment (Grades 1 and 2), since the injuries involving the posterior segment have been discussed elsewhere (Eagling, 1975). However, the figures relating to the pattern of injury and the overall visual outcome for the series as a whole are included. The figures given for the visual outcome of Grade 2 injuries differ from those previously reported (Eagling, 1975); this group was reviewed again one year later, since at the time of the first review, surgical treatment of lens damage was incomplete in many patients.

Surgical management

The surgical repair of these injuries was performed within a few hours of injury in almost all patients, and the following technique was employed: wounds were explored to their full extent; prolapsing uveal tissue was reposited if it was healthy and no infection was present, but if the iris was atonic or badly damaged or the wound was infected, this was abscised. The policy regarding a damaged lens varied: if soft lens matter was present it was washed out, but only in a small percentage of patients was immediate aspiration attempted, or complete extraction performed by an *ab externo* approach, after primary closure of the laceration. Vitreous presenting in the wound was abscised, and after wound closure with either 8·0 virgin silk sutures or 10·0 monofilament nylon sutures, the anterior chamber (or posterior segment) was reconstituted with air or saline. The follow-up period ranged from six months to five years.

Results

PATTERN OF INJURY

The age and sex distributions (Table I) show a similar pattern to those of the previous series (Roper-Hall, 1959; Johnston, 1971); the commonest injury was a simple laceration to the anterior segment (Grade 1), but a significant proportion (25 per cent) had the worst category of injury (Grade 4).

The aetiology of the injuries in this series compared with that of a similar series from this hospital of 17 years ago (Roper-Hall, 1959) is presented in Table II. There has been a dramatic increase in the number of perforating eye injuries

Address for reprints: Miss E. M. Eagling, FRCS, Birmingham and Midland Eye Hospital, Birmingham

Table I *Age and sex incidence, and the spectrum of injury*

Age (years)	*No.*	*Percentage*	*Spectrum of injury*		
			Grade	*No.*	*Percentage*
0–10	59	26			
11–20	62	27			
21–30	50	22	1	97	41
31–40	26	11	2	43	18
41–50	15	7	3	37	16
50+	16	7	4	60	25

Sex ratio:
Males = 178, Females = 50—male preponderance of 3·5 : 1

Table II *Aetiology (including a comparison with the previous series from this hospital)*

Cause	*No.*	*Percentages* 1976	1959
Road accident	72	31	2
Child play	61	26	27
Occupational	36	15	41
Domestic	34	14	20
Assault, bombs	19	8	1
Outdoor	9	4	6
Sport	6	2	3

caused by road accidents and, with the exception of one bomb-blast victim, all the bilateral perforations were from this cause. Conversely, the incidence of occupational injuries has fallen considerably.

OVERALL VISUAL OUTCOME

Table III gives the visual outcome for each grade of injury, and for the series as a whole: as expected, very few eyes with injuries confined to the anterior segment lost all useful vision, and these were due to established infection from delayed presentation. For injuries involving the posterior segment only (Grade 3), the visual outcome was predominantly good, and those who eventually lost all useful vision did so as a result of late traction retinal detachment. The combined anterior and posterior segment injuries (Grade 4) had the worst outcome, but many of these had no visual potential before repair. The factors contributing to a poor outcome for Grade 3 and 4 injuries, and the suggested management, have been discussed in detail elsewhere (Eagling, 1975).

Only one patient in the whole series developed sympathetic ophthalmitis, representing an incidence of less than 0·5 per cent. The injury in this patient was from a dart, with both lens and posterior segment damage, but the immediate postoperative course was satisfactory with 6/12 vision, and the development of sympathetic ophthalmitis had not been anticipated.

OUTCOME OF ANTERIOR SEGMENT INJURIES

Grade 1 *injuries* (97 injured eyes)

This group of patients had corneal or scleral lacerations confined to the anterior segment, without lens damage. Although 94 per cent of patients in this group achieved 6/12 vision or better when corrected, problems arising from corneal scarring and astigmatism detracted from the final outcome.

A vascularized scar was often a complication of an anterior synechia to the wound: 69 patients from this group, who presented with either an iris prolapse or with iris incarceration in the wound, were studied to see if the position of the wound, and the surgical management of the iris prolapse influenced the subsequent incidence of anterior synechiae: the results are presented in Table IV. Both factors were found to affect this: a wound crossing the limbus had a higher incidence of anterior synechiae compared with central wounds:

Table III *The overall visual outcome*

	Grades 1	2	3	4	*Total*
Good outcome (percentage) 6/6–6/12 corrected	94	65*	77	18	68*
Bad outcome (percentage) Inaccurate perception of light—excised	1	2	17	60	18

*Figures revised from those reported previously, see text

Table IV *The incidence of anterior synechiae in relation to wound position and surgical management of uveal prolapse*

	Wound				
	Limbal:		*Central:*		
Iris	*Anterior synechia*	*Nil*	*Anterior synechia*	*Nil*	*Total*
Abscised	4	12	0	5	21
Reposited	17	11	4	16	48
Total	21	23	4	21	69

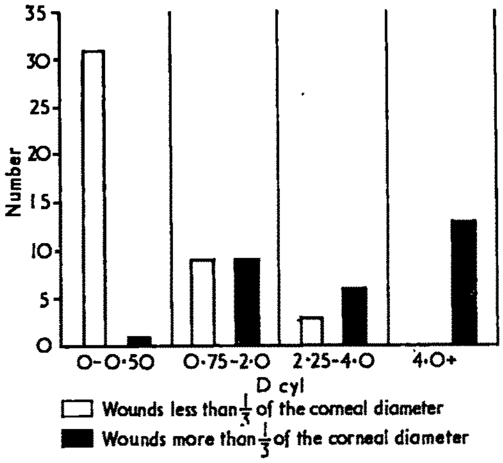

FIG. 1 *Wound astigmatism related to the size of the corneal laceration, Grade 1 injuries*

synechiae occurred more frequently after repositing an iris prolapse as compared with abscision.

Wound astigmatism, requiring either spectacle or contact lens correction, affected half the patients in this group. The principal factor contributing to this was wound size (Fig. 1); patients with lacerations involving less than one-third of the corneal diameter had a low incidence of astigmatism and many achieved good vision unaided, while those with lacerations exceeding one-third of the corneal diameter had significant astigmatism requiring correction to achieve good vision; a third of the latter had astigmatism exceeding 4·0 dioptres, and in some patients, the error was as high as 10·0 dioptres. However, with the exception of two young children, who had become amblyopic, all these could be corrected to 6/12 vision or better, and corneal grafting was not required.

The 30 patients with lacerations exceeding one-third of the corneal diameter were studied further to see what other factors might be involved: the incidence and degree of astigmatism was no greater for those patients with complete transverse lacerations as compared with those affecting one-third to two-thirds of the corneal diameter. The shape of the laceration was not a significant factor: linear lacerations were present as often as flap or complex lacerations, and astigmatism was associated with axial and peripheral lacerations alike. Of the 13 patients with astigmatism exceeding 4·0 dioptres, only one had a heavily scarred wound from an extensive anterior synechia, while the remainder had fine, fairly regular scars. A study of the axis and power of the astigmatism in six of these patients in whom the wound crossed the visual axis indicated that relative flattening had occurred along the wound and to a lesser extent across the wound; the transverse lacerations had astigmatism requiring high minus cylinders with the axis at 90° to the wound, while a laceration affecting one radius only had high mixed astigmatism with the axis obliquely related to the wound (Fig. 2).

Grade 2 injuries (43 injured eyes)

This group consisted of patients with anterior segment injuries involving lens damage who were studied particularly in relation to the functional outcome.

Table V gives the corrected vision (after a minimum follow-up period of 18 months) in relation to the age of the patient at the time of the injury: there were still four patients requiring further surgery to obtain clear media, and one who had required enucleation after panophthalmitis. With these exceptions, almost all the patients over the age of seven achieved 6/12 vision or better. For this age group, the timing of lens surgery did not affect the ultimate visual acuity; however, in the 8- to 12-year-old group, manifest squints developed rapidly, even in those in whom clear media and contact lens fitting had been achieved within three months of injury. In the older patients successfully fitted with a contact lens, 12 out of 20 patients complained of diplopia, even after a prolonged period of wear, and seven of these have given up

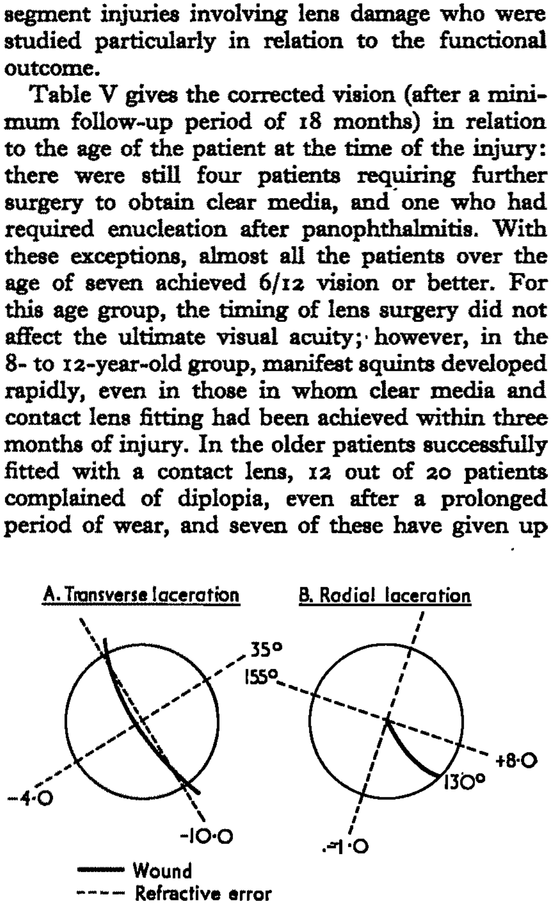

FIG. 2 *Examples of astigmatism showing power and axis in relation to the wound*

Table V *The visual outcome for Grade 2 injuries in relation to age at the time of injury*

Visual acuity	*Age (years)*		
	<8	8–12	>12
6/6–6/12	1	5	22
6/18–6/36	4	1	2
6/60–perception of light	3	1*	3*
Excised	0	0	1

*Further surgery required to achieve clear media contact lens wear for this reason. The time taken to achieve clear media and contact lens fitting did not influence this. By contrast, four patients with Binkhorst intraocular lenticuli have no problems with diplopia.

The outcome was far less satisfactory for the children under eight years of age: all rapidly developed manifest squints and, with one exception, all have developed dense amblyopia and suppression. Although five of these children had clear media within four months of surgery, treatment by contact lens, Binkhorst intraocular lens or spectacle correction, and occlusion, was not successful in fully reversing this.

Discussion

When the overall outcome of this series is compared with that of a similar series reported from this hospital 17 years ago (Roper-Hall, 1959), it can be seen that a much higher percentage of patients (68 per cent in 1976; 45 per cent in 1959) are achieving 6/12 vision or better. This largely reflects the better outcome of anterior segment injuries. However, the studies undertaken on this type of injury indicate that there is room for further improvement.

Problems relating to the wound—that is, corneal scarring and vascularization associated with anterior synechiae, and wound astigmatism—were studied in the group of patients without lens damage. Anterior synechiae occurred most frequently after repositing an iris prolapse through a wound encroaching on the limbus; Mackensen (1970) emphasized the importance of repositing an iris prolapse through a separate incision, and ensuring a watertight (as opposed to airtight) wound. As atonicity of the prolapsed iris may allow postoperative contact with the wound peripherally, even if the depth of the anterior chamber is maintained, a peripheral iridectomy through the extremity of a wound encroaching on the limbus is recommended.

Wound astigmatism characterized lacerations exceeding one-third of the corneal diameter: a study of those patients with high degrees of astigmatism suggested that flattening along the wound was responsible for this. Although the process of healing may necessarily cause this to some degree, the very high astigmatic errors must reflect some failure of surgical technique. Flattening of a wound indicates inversion and reflects inadequate suture depth with overtightening; however, in a retrospective study of this nature details such as suture depth were not recorded, and this will require further study on a prospective basis.

Despite these complications related to the wound, the corrected visual outcome for this group was good, and no patient has required corneal grafting.

In the group of patients with anterior segment injuries associated with lens damage, although the corrected vision in those patients of eight or more years was good, the number of patients achieving comfortable vision with contact lens correction was disappointing. The use of intraocular lenticuli may offer a better chance of binocular vision in patients with unilateral aphakia (Girard, Friedman, Moore, Blau, Binkhorst, and Gobin, 1962), and although the numbers treated in this way in this series are small, the results are encouraging.

For the children under eight years, the visual outcome was poor because of amblyopia, despite attempts to reverse this. Even with immediate lens surgery at the time of injury or shortly after, it was difficult to achieve clear media within two months of injury, and by this stage, the amblyopia in young children was very difficult to reverse, even when dealing with the best optical situation with an intraocular lens. The prognosis for this age group in terms of a functional outcome remains poor.

In relation to the question of timing of lens surgery, it was apparent from studying the patients' records that it was not always easy to be certain whether lens damage was present at the time of repair; a layer of fibrin covering the lens capsule in the pupil region may be mistaken for a cataractous lens. If there is doubt, and the posterior segment is not involved, lens surgery can safely be delayed for a few days. In young children, although a damaged lens will spontaneously absorb, early deliberate surgical intervention to achieve clear media as quickly as possible is the only hope of preventing irreversible amblyopia.

Where the extent of damage cannot be visualized because of hyphaema, it is vital to remove this by gentle irrigation with either saline or a fibrinolytic agent, in order to ascertain the extent of the damage. In the absence of involvement of the posterior segment (manifested by vitreous loss), it is less essential to deal with a damaged lens at the time of primary repair, although immediate lens surgery helps to reduce postoperative inflammation; if, however, vitreous loss is present in association with lens damage, it is essential to undertake immediate and radical lens surgery in conjunction with anterior vitrectomy, as the admixture of a damaged lens (especially capsule), vitreous, and blood rapidly leads to anterior segment organization, resulting in phthisis and subsequent retinal detachment (Coles and Haik, 1972; Eagling, 1975).

Conclusions

This study has shown that although the visual outcome for perforating injuries involving the anterior segment has considerably improved during the last 17 years, there remain problems associated with wound scarring and astigmatism, and with traumatic aphakia; for the former, avoidance of anterior synechiae by performing a peripheral iridectomy when repositing an iris prolapse through a wound extending to the limbus, and accurate suturing centred on and transfixing the deepest part of the wound may help to reduce these complications. For the latter, the functional outcome has proved disappointing, particularly in young children; whether the use of intraocular lenticuli can improve on this remains to be seen.

I thank my colleagues at the Birmingham and Midland Eye Hospital for permission to review their patients. I also thank Miss L. Bayliss and Mr R. Carter for technical help.

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Prognosis of perforating eye injury

H. P. ADHIKARY, P. TAYLOR, AND D. J. FITZMAURICE
From the Department of Ophthalmology, Royal Infirmary, Preston

The general prognosis of perforating eye injury has improved remarkably during the last two decades. It is a perplexing task to assess the prognosis in view of the variations in the severity of the wound and of the intraocular damage, as well as the great diversity of complications which may arise.

In this series, 130 cases of perforating globe are presented and a significant improvement in the overall position is revealed.

Material and methods

This series constituted 130 consecutive cases of accidental perforating eye injuries, including 22 with intraocular foreign bodies. Patients were treated in the Eye Department, Preston Royal Infirmary, and were followed-up at the clinic for a period varying between three months and four years, the last case being in November 1975. Patients who failed to attend for follow-up and some who were referred from other hospitals were excluded because full details during the follow-up period were lacking. Out of 130 cases, 20 (15·4 per cent) were women and 40 (30·7 per cent) were children, seven of whom were girls.

Injuries were mainly caused by road accidents, a fall on the ground, an accident with chisel and hammer, assault with fist or other blunt objects, gun-shot injury, or, particularly in children, by pointed objects such as a stick or branch of a tree, or a dart, arrow, or needle. Some injuries had been inflicted by less common objects such as a fish hook with a maggot on it, the edge of a sheet of paper, or water jet, etc. (Table I).

The site and extent (Table II) of injury observed varied from a small penetrating injury of single line 1 mm in length of cornea or sclera to major extensive ramified lacerations across the whole diameter of the cornea and almost the whole length of the sclera, with laceration, incarceration, avulsion, and even expulsion of uveal tissue, lens, and vitreous humour. In one patient the posterior portion of the globe behind the equator was almost completely separated from the rest of the eye ball.

The degree of injury and severity of damage to the ocular structures was classified as follows:

FIRST DEGREE

Perforating injury of any length of cornea or sclera varying from a minute puncture to the whole diameter of cornea, without lens injury, uveal or vitreous prolapse, without intraocular foreign body.

SECOND DEGREE

Injuries of any size to cornea or sclera with lens injury, or uveal, vitrous prolapse, or with intraocular foreign body.

THIRD DEGREE

Double perforation of the globe caused by gun-shot or other metallic particles, extensive ramified lacerations of the anterior segment, laceration of the posterior pole, and injuries with massive haemorrhage leading to vitreous disorganization.

The incidence of the types of injury is shown in Table III. On first admission 80 cases (61·5 per cent) were found to have uveal tissue either incarcerated in the wound or prolapsed. In some patients the tissues were reposited and in others tissue had to be abscised during repair. Seventy-six cases (58·4 per cent) needed treatment for traumatic cataract. During the follow-up

Table I *Causes of injury*

Patients	*Road accident*	*Chisel and hammer*	*Flying objects*	*Assaults*	*Blunt objects*	*Pointed objects*	*Others*
No.	26	16	18	9	19	20	22
Percentage	20	12·3	13·8	6·9	14·6	15·4	16·9

Table II *Site of injury*

Patients	*Corneal (single or ramified laceration)*	*Scleral (single or ramified laceration)*	*Corneo-scleral (radial single line or ramified)*	*Limbal (circum-ferential)*
No.	49	25	34	22
Percentage	37·7	19·2	26	16·9

Table III *Incidence of different degree of injury*

Patients	*Degree*		
	First	*Second*	*Third*
No.	24	75	31
Percentage	18·5	57·7	23·8

Address for reprints: H. P. Adhikary, FRCS, St Paul's Eye Hospital, Old Hall Street, Liverpool L3 9PF, Merseyside

period particular attention was paid to controlling inflammation in the affected eye, and the possible development of any anterior synechiae, secondary glaucoma, and retinal detachment; inflammatory reaction to the other eye was also looked out for. Fifty-eight cases (44·6 per cent) needed further operations during the follow-up period, such as synechiotomy, cataract extraction, needling and aspiration of lens material, drainage operation for secondary glaucoma, or surgery for retinal detachment.

Finally, assessment was made of the visual acuity obtained after correction of refractive error, either with spectacle lens or with contact lens. Enucleation was performed only in blind eyes that were not symptom-free and were cosmetically unsatisfactory or unsafe.

Results

The results are shown in Table IV.

Discussion

The prognosis of perforating lesions of the globe is uncertain because of complications, many of which depend on correct assessment, and vary in seriousness according to the time at which they occur, and the method of management. Our principles of management were aimed at securing an accurate surgical re-apposition of the wound and restoring the normal anatomy as quickly as possible, preventing or controlling infection, and maintaining and controlling the intraocular pressure within normal limits. One striking feature noted in the series was the low incidence of infection. In only three instances was intraocular reaction, caused either by infection or by the injury itself, severe enough to result in hypopyon, and in each this settled satisfactorily and the patient regained visual acuity of better than 6/12. In none was panophthalmitis or chronic endophthalmitis found to develop to warrant removal of the eye, compared with the overall infection in 15 per cent, including 38·6 per cent of all enucleated eyes (Snell, 1945) and 28·9 per cent of enucleated eyes caused by infection or vitreous abscess (Remky, Kobor, and Pfeiffer, 1967).

Table IV *Results in visual acuity for 130 patients*

Result	*Degree* 1st	2nd	3rd	*Total*	*Overall percentage*
Vision better than 6/12	21	58	3	82	63
Vision between 6/60 and 6/18	2	5	5	12	9·2
Vision less than 6/60	1	9	10	20	15·4
No perception of light cosmetically satisfactory	0	2	2	4	3
Enucleation or evisceration	0	1	11	12	9·2
Total	24	75	31	130	100

Among the 24 cases of first degree injury, three needed further operation during the follow-up period, one for anterior synechiae, one for cataract, and one for tractional retinal detachment. Twenty-one cases (87·5 per cent) retained vision better than 6/12, two between 6/60 and 6/18, and one less than 6/60.

Further operation was necessary in 40 out of 75 cases of second degree injury, mainly for traumatic cataract and anterior synechiae. If aspiration of lens material was considered to be justified, it was generally done within two weeks of the injury. Tractional retinal detachment was found in four instances and secondary glaucoma in three. In this group, 58 patients (77·3 per cent) recovered their vision to better than 6/12, five cases to between 6/60 and 6/18, nine cases to less than 6/60, two cases lost perception of light, and enucleation was performed in one.

Apart from the extensive reparative procedure carried out during the first operation, out of 31 cases of third degree injury further operation was justifiable only in eight. In the remaining patients either the lens with some vitreous was extruded during the injury and an unexpected amount of sight regained, or further surgery was not considered likely to be beneficial. In this group only three patients (9·7 per cent) regained 6/12 vision, five cases between 6/60 and 6/18, 10 cases less than 6/60, two cases lost perception of light, and enucleation was necessary in 11 eyes.

Altogether 12 eyes (9·2 per cent) were excised. In five (3·8 per cent) the eye was excised shortly after injury without any attempt at reconstruction because the eye was hopelessly damaged and was considered at the time to be unsafe to preserve and potentially dangerous for the other eye. Seven eyes were enucleated later, two for chronic haemophthalmitis after further trauma (self-inflicted) to the same eye, two for painful blind eye due to intractable secondary glaucoma, and three for phthis bulbi.

Eyes with visual acuity of between 6/60 and 6/18, could probably have been improved further by some minor procedure—such as needling—or major procedure—such as optical keratoplasty—but it was not possible to carry these out for various reasons. In 20 eyes the visual acuity decreased to less than 6/60; in five there was tractional retinal detachment, three had organized vitreous around non-magnetic, unremoved intraocular foreign bodies, and the remaining eyes had severe corneal scars, organized vitreous haemorrhages, blood-stained corneae or macular changes, either alone or in combination. Six patients were found to have secondary glaucoma. In two instances, gradual atrophy of the iris after trauma leading to complete aniridia in the course of 12 and 16 months' time was the other significant change associated with the injury.

None of the patients was found to develop sympathetic ophthalmitis.

Summary

The assessment of visual function in a series of 130 consecutive patients of perforating eye injuries, revealed that visual acuity of 6/12 or better was regained in 63 per cent, between 6/60 and 6/18 in 9·2 per cent, less than 6/60 in 15·3 per cent, and enucleation was necessary in 9·2 per cent. In 3 per cent, the eyes were retained as blind, symptom-free, and cosmetically satisfactory organs. Two eyes were found to develop complete traumatic aniridia. None in the series was found to have sympathetic ophthalmitis.

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Ocular injuries from liquid golf ball cores

D. R. LUCAS,[1] A. C. DUNHAM,[2] W. R. LEE,[3] W. WEIR,[4] AND
F. C. F. WILKINSON[2]
From the Departments of Ophthalmology,[1]*, Pathology,*[1] *and Geology*[2]*, University of Manchester, the Department of Ophthalmology, University of Glasgow,*[3] *and the Department of Pathology, Royal Alexandra Infirmary, Paisley*[4]

Cutting up golf balls, usually by children, has long been recognized as an ocular hazard as many golf balls contain fluid under high pressure which is liable to strike the eye (Duke-Elder, 1954). In some of the early cases, serious loss of vision resulted (Crigler, 1913; Lowell, 1913; Thomason, 1913). The early golf balls contained barium sulphate, soap, and free alkali (Crigler, 1913). The alkali was presumably responsible for the serious ocular injuries and, after 1914, it was no longer used in the manufacture of golf balls in the United States of America. Barium sulphate is still, however, a major constituent of recently manufactured golf balls, at least in the UK.

Twelve cases of injury to the eyelid, conjunctiva, and orbit resulting from disrupted golf balls have been reported during the last 10 years (Table I).

Address for reprints: D. R. Lucas, Department of Ophthalmology, Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH, *or* A. C. Dunham, Department of Geology, Williamson Building, The University, Manchester M13 9PL, *or* W. R. Lee, Tennent Institute of Ophthalmology, Western Infirmary, Glasgow G11 6NT

Table I *Published cases of injuries from golf ball contents*

Authors	*Cases*	*Age (years)*	*Sex*	*Time between injury and excision*	*Site(s) of injury*	*Follow-up*
Johnson and Zimmerman (1965)	1	11	Male	11 days	Conjunctiva*	
Penner (1966)	1	11	Male	1 year	Lower lid* and orbit	Satisfactory after excision of mass one year after accident
	2	10	Female	—	Face, no penetration	
Slusher and others (1967)	1	11	Male	5 days	Conjunctiva* and cornea	Satisfactory after excision
	2	15	Male	Hours	Conjunctiva	Satisfactory after removal of pasty material by applicator
	3	12	Male	Hours	Conjunctiva and cornea	
	4	9	Male	Hours	Conjunctiva and cornea	Satisfactory after excision
Taylor and Greer (1969)	1	12	Male	6 months	Conjunctiva*	Uneventful
	2	12	Female	6 weeks	Conjunctiva* and cornea	—
Nelson (1970)	1	22	Male	Not stated	Conjunctiva and cornea	Traumatic mydriasis 9 months after accident
	2	31	Male	Not stated	Cornea	
O'Grady and Shoch (1973)	1	13	Female	2 months	Conjunctiva*	Uneventful

*Histological findings on excised tissue reported

Table II *Details of nine cases*

Case	*Age (years)*	*Sex*	*Injury to excision period*	*Nature of explosion*	*Site*	*Follow-up*
1	12	Male	18 hours	Disruption of golf ball	Subconjunctiva	Uneventful
2	8	Male	< 48 hours	Stuck a knife into a golf ball	Right supero-nasal bulbar conjunctiva	Pseudopterygium
3	11	Female	< 48 hours	Hacksaw used to open golf ball in a vice	Xanthelasma-like lesion left upper eyelid with deposit in fornix	Severe oedema of lid. Residual scar. Intermittent conjunctivitis
4	12	Male	5 days	Cutting into golf ball	Small white mass in left supero-temporal conjunctiva. Commotio retinae	Uneventful Chorioretinal scar
5	12	Female	6 days	Stuck a knife into a golf ball	Inferior bulbar conjunctiva	Uneventful
6	13	Male	7 days	Focused sun's rays on a golf ball	Supero-nasal bulbar conjunctiva* Eyelid	Uneventful
7	10	Male	18 days	Cut up golf ball	Right bulbar conjunctiva three nodules in substantia propria on nasal side	Betamethasone
8	13	Male	16 weeks	Cut up golf ball	Black deposits in left supra-bulbar conjunctiva	Uneventful
9	11	Male	20 weeks	Golf ball 'exploded' in face	Punctate staining of cornea; subconjunctival white mass on lower temporal bulbar conjunctiva	Small residual nodule

*Blanching of the conjunctiva in upper nasal quadrant looked like a local corticosteroid injection

Most of the injured were boys, aged between 10 and 13 years. Histological studies of six cases (Johnson and Zimmerman, 1965; Penner, 1966; Slusher, Jaegers, and Annesley, 1967; Taylor and Greer, 1969; O'Grady and Shoch, 1973) revealed birefringent granules with multinucleate giant cells and macrophages. In three cases (Johnson and Zimmerman, 1965; O'Grady and Shoch, 1973) analysis of the foreign material by histochemistry, *x*-ray diffraction, and the electron probe demonstrated the presence of barium sulphate and zinc sulphide.

The opportunity to study a further nine cases has permitted a more detailed analysis of the tissue response between 18 hours and 20 weeks. In addition, the foreign material in some of the specimens has been studied by applying the electron probe to thick paraffin sections of the biopsied material and, for comparative purposes, the contents of several brands of golf ball have also been analysed.

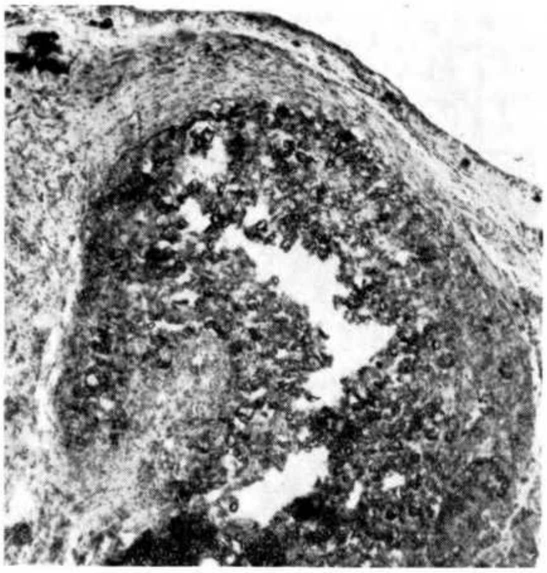
Methods

LIGHT MICROSCOPICAL EXAMINATION

The tissue was prepared by conventional histological methods.

ELECTRON PROBE ANALYSIS

20-μm sections were cut from the paraffin blocks from which the sections for light microscopical examination



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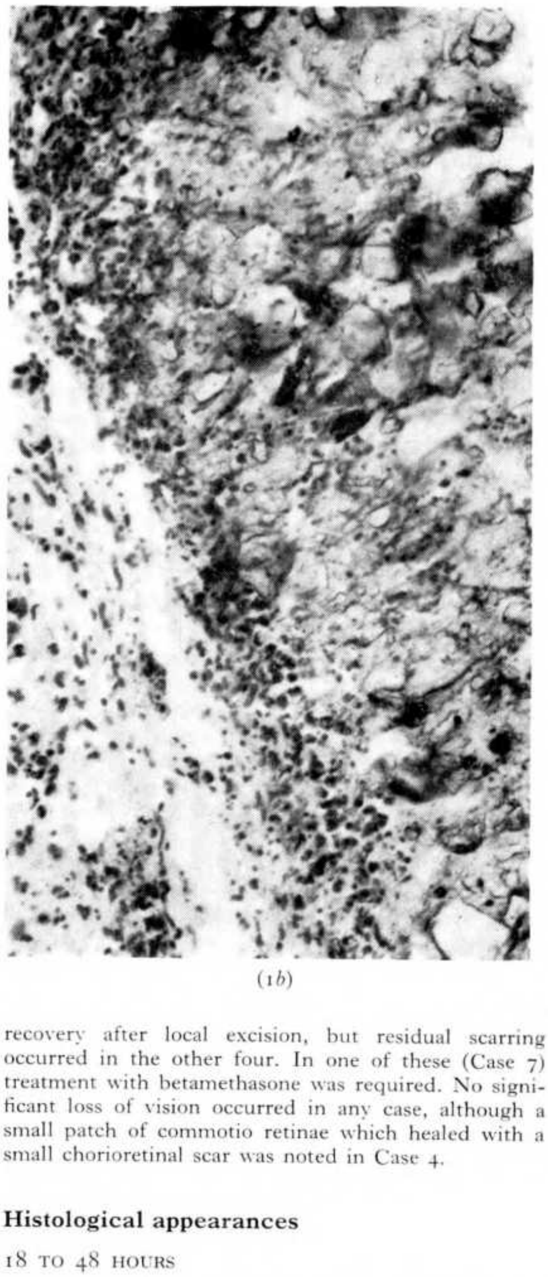


(1*b*)

FIG. 1 *Conjunctiva 18 hours after accident (Case 1).* (*a*) *Large well circumscribed deposit of crystalline material in substantia propria. Haematoxylin and eosin.* × 50. (b) *Pyknotic debris around the deposit. Haematoxylin and eosin.* × 250

had already been taken. These were mounted on glass slides 5·1 × 2·5 cm (2 × 1 in) and coated with carbon after removal of the wax. The samples were investigated using a Cambridge Scientific Instruments Geoscan Mark II.

X-RAY DIFFRACTION AND X-RAY FLUORESCENCE OF GOLF BALL CONTENTS

The slurry from the centres of nine different types of golf ball was extracted using a hypodermic syringe. In several cases the pressure of the slurry was enough to force the piston right out of the syringe. The slurry was then dried and the solid residue examined by transmitted and reflected light techniques and by x-ray diffraction. Smear mounts of the dried slurry were examined in a Phillips diffractometer.

Semiquantitive analysis of two dried slurries was made using a Phillips x-ray fluorescence machine.

Cases

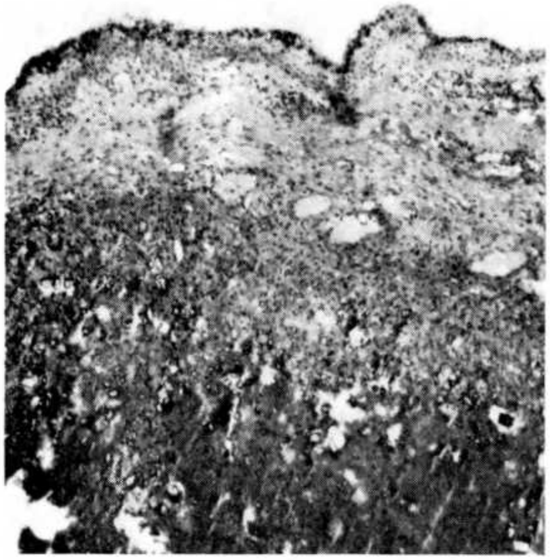
Details of the nine cases are set out in Table II. In all cases, conjunctival lesions were present; in two (Cases 3 and 6) the eyelid was also involved. In Case 8 the deposits were black, but in all others they were creamy-white.

In five cases, there was complete and uneventful recovery after local excision, but residual scarring occurred in the other four. In one of these (Case 7) treatment with betamethasone was required. No significant loss of vision occurred in any case, although a small patch of commotio retinae which healed with a small chorioretinal scar was noted in Case 4.

Histological appearances

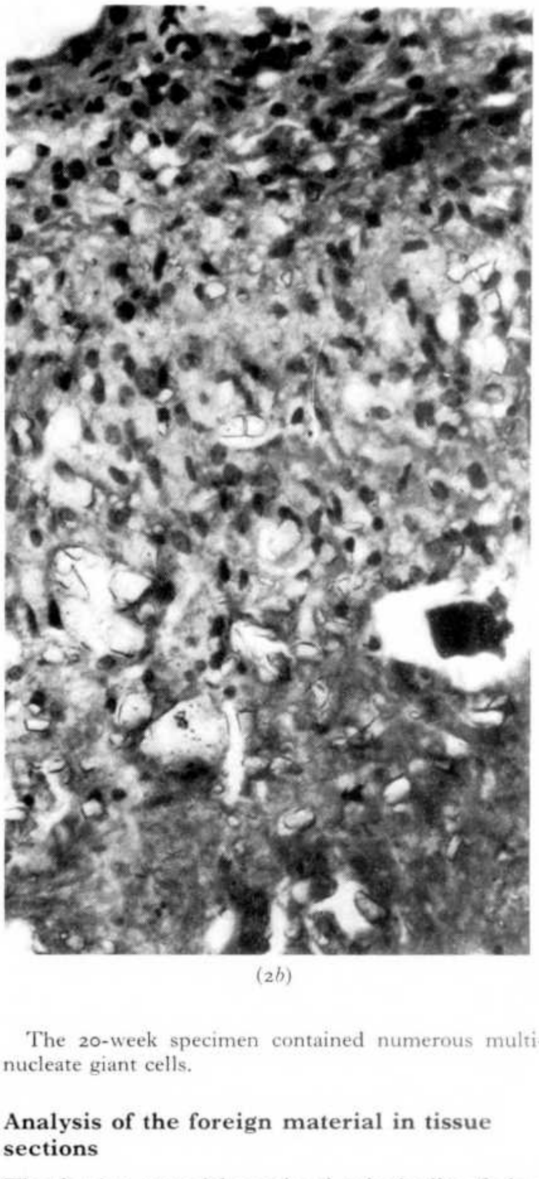
18 TO 48 HOURS

The deposits of crystalline material and other foreign matter were present in large pools in the substantia propria of the conjunctiva, in the dermis, and in the orbicularis muscle. These pools contained some necrotic debris and red cells and were surrounded by a thin rim of polymorphs and lymphocytes. Many of these cells showed nuclear pyknosis and numerous free nuclear fragments were also present (Fig. 1). In one (Case 3) birefringent material was observed in macrophages. The Prussian blue reaction demonstrated some iron-containing crystalline material in the debris.



(2*a*)

FIG. 2 *Conjunctiva five days after accident (Case 4).*
(a) *Deposit of crystalline material in substantia propria surrounded by a well defined layer of macrophages. Haematoxylin and eosin.* ×50
(b) *Palisade-like arrangement of crystal-containing macrophages in the layer. Haematoxylin and eosin.* ×250



(2*b*)

5 TO 18 DAYS

In the four cases in this group, the centre of the deposit still contained amorphous necrotic debris around the birefringent material. At the periphery, there was a cellular infiltrate composed predominantly of lymphocytes and macrophages. The macrophages formed a distinctive palisade between the deposit and adjacent tissue in three cases (4, 5, and 7, Fig. 2). In the eyelid tissue from Case 6, the cellular reaction was particularly diffuse, presumably because the crystals were widely scattered in the dermis. Very small crystals were observed in the cytoplasm of the macrophages while the larger crystals were surrounded by small flattened multinucleate cells (Fig. 3). Even at this stage, perivascular accumulations of macrophages containing birefringent crystals could be seen.

Palisading of macrophages was prominent in the 18-day specimen.

16 TO 20 WEEKS

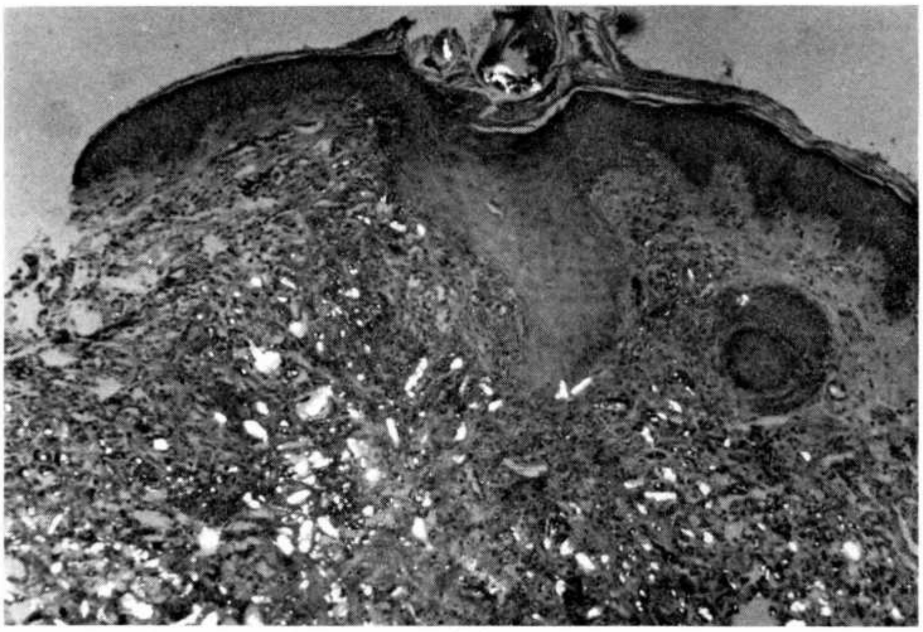
The crystalline and other foreign matter was embedded in a delicate fibrovascular stroma to form a clearly circumscribed mass in the 16-week specimen (Fig. 4*a*). In this case many black particles were present. Numerous macrophages and multinucleate giant cells were present in the stroma and strands of histiocytes containing small particles were seen lying along small blood vessels (Fig. 4).

The 20-week specimen contained numerous multinucleate giant cells.

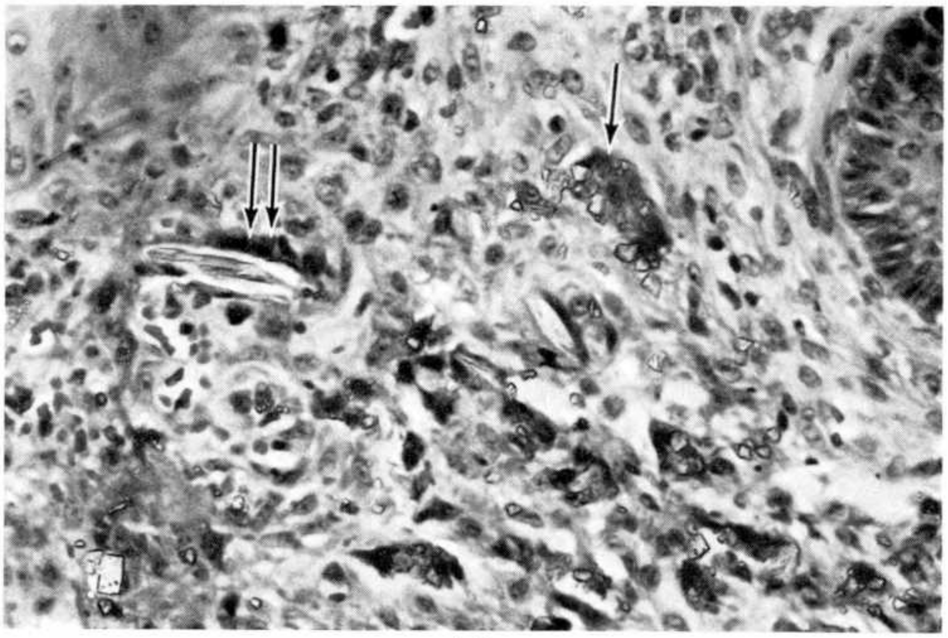
Analysis of the foreign material in tissue sections

The foreign material consisted principally of clear or pale-staining birefringent crystals varying considerably in size in different specimens (Figs 1–4*b*). In addition, semi-opaque brownish-black particles varying in size and shape were present. The amount of this material differed greatly in different specimens. Some contained hardly any, while in Case 8 the amount was sufficient to account for the almost black appearance of the deposits.

The birefringent crystals were frequently almost square (rhombic, angles 80° and 110°) (for example, Figs 1 and 2*b*). Under crossed polars the extinction position indicated that the principal optical directions lay along the diagonals of the rhomboid

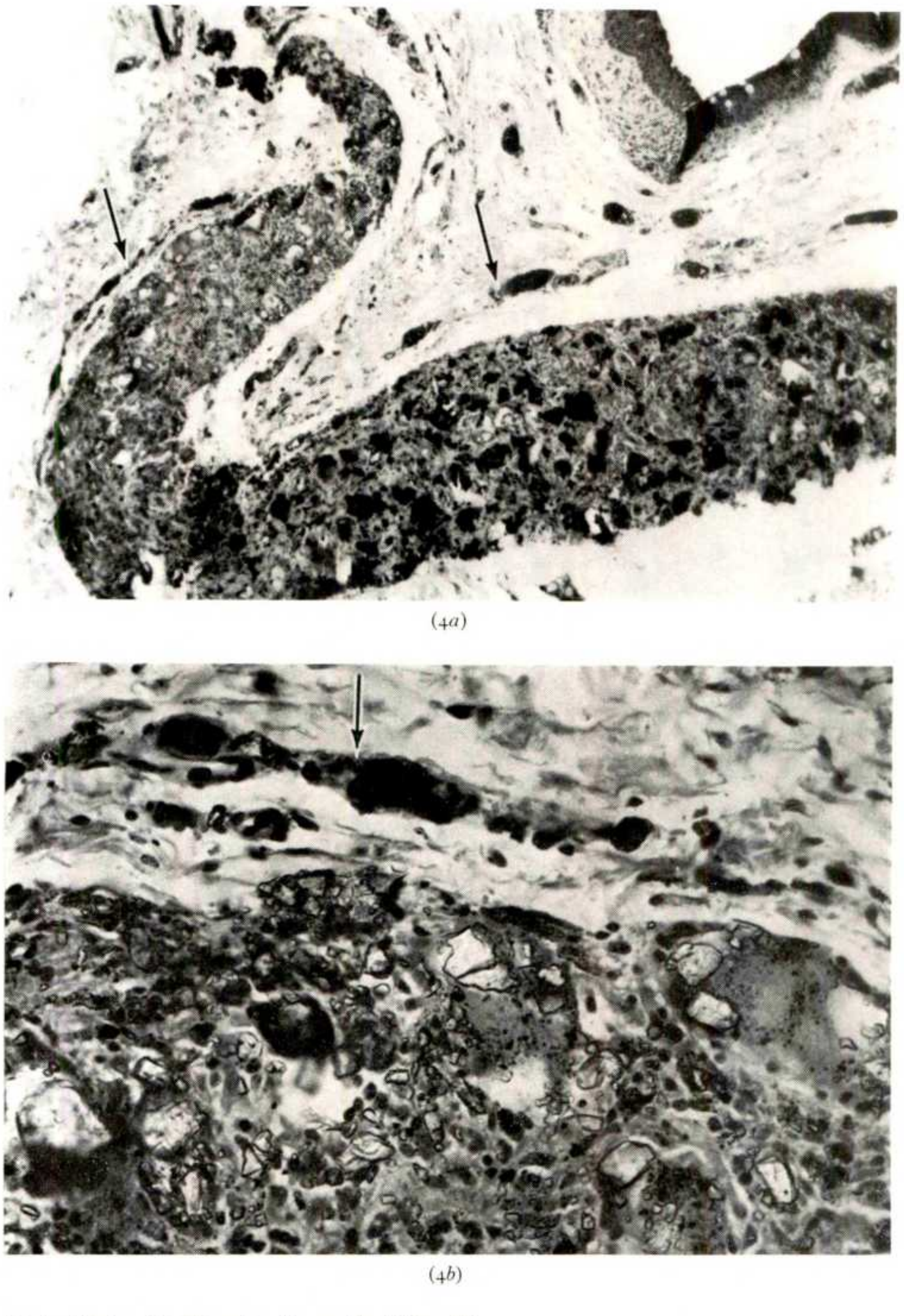


(3*a*)



(3*b*)

FIG. 3 *Eyelid seven days after accident (Case 6).*
(a) *Diffusely scattered crystals in the dermis. Haematoxylin and eosin.* ×50, *under polarized light.*
(b) *Light diffuse infiltration of dermis with inflammatory cells, giant cells containing small crystals (single arrow) and flattened giant cells around large crystals (arrows). Haematoxylin and eosin.* ×250


(4*a*)

(4*b*)

FIG. 4 *Conjunctiva* 16 *weeks after accident (Case* 8*).*
(a) *Deposits of crystalline and black material in substantia propria embedded in fibrovascular stroma. Strands of macrophages laden with foreign material present along blood vessels (arrows). Haematoxylin and eosin.* × 50.
(b) *Macrophagic reaction in stroma and perivascular macrophages containing foreign material (arrows). Haematoxylin and eosin.* × 250

Table III *Partial electron probe analysis of barytes*

	*Pulses/unit time for barytes**		
	Case 3	*Case* 5	
		Block 1	*Block* 2
Barytes standard	8745	3673	8745
Sample	7496	3561	8634

*S was also present in all cases, but was not analysed quantitatively

Table IV *Comparison of electron probe analysis of dark particles in Case* 8 *with published composition of hydromuscovite and muscovite* (*Deer, Howie, and Zussman*, 1966)

Dark particles	*Case* 8	*Hydromuscovite*	*Muscovite*
SiO_2	46·7	46·5	48·4
Al_2O_3	33·9	36·4	27·2
K_2O	10·7	8·1	11·2
Fe Oxide	2·6*	0·7†	7·4†
MgO	Present	0·5	0·0
Na_2O	Present	0·5	0·4
H_2O	Not known	6·8	4·5
Σ	93·9	99·5	99·1

*as FeO
†as FeO + Fe_2O_3

shapes. The optical data indicate that the crystals are crushed barytes ($BaSO_4$), whose shape is controlled by cleavage along the (210)* faces.

Quantitative microprobe analysis by the use of the crystal spectrometers (Table III) showed that barytes was the major constituent of the foreign material ($>$90 per cent).

The semi-opaque, brownish-black particles often appeared hexagonal (Fig. 4*a*). They were much thinner than the section of tissue (20 μm) and showed very low birefringence which, in some cases, was masked by the dark brown colour. Microprobe analysis proved the particles to be muscovite or hydromuscovite (Table IV).

A single grain of pyrite and several grains of iron oxide were found in Case 8 by microprobe analysis.

No zinc-bearing grains were detected.

Analysis of golf balls

Eight out of the nine slurries from the centre of the balls were white, while the ninth was black. Microscopical examination of the dried slurries showed the presence of large amounts of barytes, with shapes and sizes very similar to those found in the granulomata. The dark hexagonal grains were also present in small quantities. The dark-coloured slurry differed only in having a dark-coloured fluid medium.

X-ray diffraction charts of all nine samples were identical; the only mineral showing up in the trace was barytes. This suggests that the muscovite may be poorly crystalline and hence would not produce *x*-ray diffraction. The amount of the muscovite is also small ($\sim$5 per cent). Partial *x*-ray fluorescence analyses of two samples were made. These were very similar except for the content of Sr (Table V) which is no doubt related to the source of the barytes used by the different manufacturers. The Pb reported in the analysis is probably present as galena (PbS).

Discussion

Most golf balls manufactured in this country still contain a liquid centre under high pressure. The particulate material in the liquid is capable of penetrating both conjunctiva and skin if the rubber casing of the liquid centre is perforated by the unwary. The mineral assemblage found in this material and in the tissue sections from those injured (barytes, muscovite, galena, pyrite, and iron oxide) is typical of natural barytes deposits. The barytes was in the form of crushed crystals. In the American cases, the crystalline material was apparently barium sulphate and zinc sulphide (Johnson and Zimmerman, 1965; O'Grady and Shoch, 1973) and the birefringent crystals were white in unstained sections, and the lesions did not appear to be pigmented grossly. The material was thought to have been derived from lithopone, which is a mixture composed of 70 per cent $BaSO_4$ and 30 per cent ZnS, but Johnson and Zimmerman (1965) failed to identify zinc by *x*-ray microanalysis.

Table V *X-ray fluorescence analysis of dried slurry from a Dunlop* 65 *golf ball*

SiO_2	5·8
Al_2O_3	2·8
FeO	0·4
MgO	0·1
CaO	0·1
Na_2O	$<$0·1
K_2O	0·1
Sr	0·28 (1·00)*
Pb	1·00
Zn	0·1
Ti	0·1
Mn	$\ll$0·1
Ba	Abundant
S	Abundant

*Penfold Club ball

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*Miller index

They attributed the failure of matrix effect in the sample to the large mass absorption coefficient of Ba. However, in experiments with a mixture of 30 per cent ZnS and 70 per cent $BaSO_4$ (Dunham and Wilkinson, unpublished) in which an *x*-ray diffractometer rather than a powder camera was used, it was found that, of the four principal *x*-ray peaks shown by ZnS, three were coincident or very close to the $BaSO_4$ peaks, but the fourth was quite distinct. The matrix effect did not mask the ZnS.

Sections from Johnson and Zimmerman's material were subjected to electron probe *x*-ray microanalysis and zinc was detected in addition to barium and sulphur (Johnson and Zimmerman, 1965).

Doubt thus remains as to the exact identity of the crystalline material in the American cases, although the major ingredient was, as in our cases, $BaSO_4$. The brown or black particles in our cases were separate mineral particles which electron probe analysis showed to be of the mica group. Zinc was present only in trace quantities.

The histological response of the tissues to $BaSO_4$ crystals differs in some respects in our cases from previous accounts. In cases examined within a few days of injury, we observed a mild inflammatory response as described by Johnson and Zimmerman (1965) and Slusher and others (1967), but not the distension of macrophages by small particles emphasized by these authors. Within a few weeks, evidence of inflammation and tissue necrosis had disappeared and there was progressive tissue fibrosis. Comparable changes were observed by Penner (1966) and Taylor and Greer (1969). However, no previous mention has been made of the macrophage migration to adjacent blood vessels which was presumably part of an ineffectual attempt to remove foreign material.

An interesting feature of the condition is the great variation in the interval between occurrence of the accident and the appearance of the patient for treatment. This may depend on the intensity of the immediate conjunctival reaction. This reaction probably depends on the nature of the organic binding material which is always present in the golf ball centres and which we have not attempted to identify.

Deposition of crystals in the cornea occurred in six of the 12 published cases. In three there was transient loss of vision (Slusher and others, 1967) and in two there was significant residual disability (Nelson, 1970). In our cases, significant corneal damage was not recorded. Since the cornea represents a large centrally situated area to which the trajectory of the particles must approximate most closely to the perpendicular and thus favour penetration, it is surprising that corneal damage is not a regular feature. The resistance of the cornea may be due to tight epithelial adhesion to Bowman's membrane, the mechanical strength of which probably prevents deep penetration. The substantia propria of the conjunctiva and the dermis of the eyelid are, by contrast, lax tissues.

Finally, the study has demonstrated the relative ease with which individual mineral particles can be identified by means of the electron probe in thick paraffin tissue sections.

Summary

Tissue removed from nine new cases from 18 hours to 20 weeks after injury by a golf ball contained crystalline and other foreign material to which there was a mild inflammatory reaction followed by macrophagic activity and fibrosis.

Optical and electron probe analysis showed that the crystalline material was crushed barytes containing small quantities of muscovite as is typical in natural deposits. The centres of several golf balls were shown to contain essentially identical material. By contrast with previous reports, no zinc sulphide was found.

The form and frequent location of the deposits in the conjunctiva as compared with cornea and eyelid is related to the structure of these tissues.

We thank the ophthalmic surgeons in the Glasgow and Manchester regions for permission to publish clinical details of their cases and Mr D. Bradley and Mr G. Humberstone for skilled technical assistance in the preparation of the thick sections and the illustrations.

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Traumatic cyclodialysis
A case report

E. AVIEL AND R. AVISAR
From the Barzilai Medical Centre, Ashkelon, Israel

Traumatic cyclodialysis has been reported by several authors during the last decade (Sedan, 1966; Turut, Constantinides, and Asseman, 1971). Romem and Singer (1973) described a case of traumatic aniridia without prolapse of iris through an external wound. Trobe and Keeney (1974) reported three cases of traumatic aniridia all of which were accompanied by perforating wounds involving the cornea.

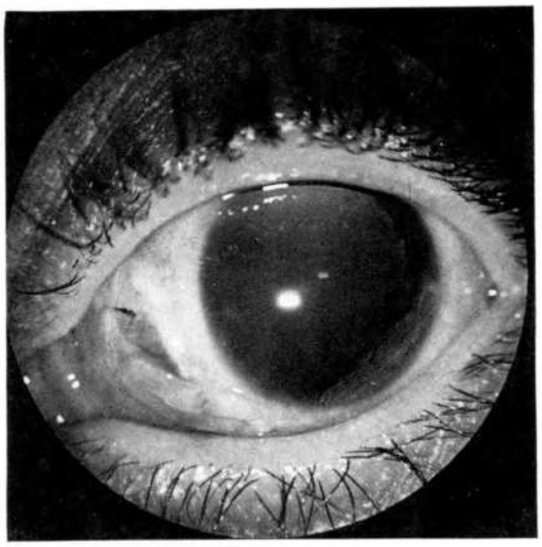
This is a report of a case of traumatic cyclodialysis with extrusion of most of the iris through a scleral perforation.

Case report

A 25-year-old White female agricultural worker was admitted to the ophthalmic department of the Barzilai Medical Centre, Ashkelon, after an injury to her left eye caused by a screwdriver (Figure). The injury had been accidentally self-inflicted two hours earlier as she had been trying to repair a tubing of metal in the cow-shed.

The visual acuity in the right eye was 6/6, and examination of that eye including the fundus revealed nothing abnormal. The visual acuity in the left eye was hand movements with good perception of light. The upper lid was swollen with ecchymoses and abrasions of the skin. There was conjunctival injection. On the medial side about 4 mm from the limbus, a brown oval mass could be seen under the abraded conjunctiva. The cornea was clear and did not show any signs of perforation. The anterior chamber was filled with blood and it was impossible to see any further details. The eye was hypotonic, tension by Schiötz tonometry was 5·5/16.

It was decided to proceed with exploration of the ocular injury under general anaesthesia. An operation was performed on the day of admission. On exposure of the sclera medially, a mass of soft brown tissue was seen within the scleral wound which extended along a course roughly parallel to the limbus from 7.0 o'clock 3 mm from the limbus to 10.0 o'clock 9 mm from the limbus. It was necessary to separate the medial rectus from its insertion to obtain adequate exposure of the scleral wound. The brown mass was identified as prolapsed iris and it was excised level with the sclera. After the excision the intact ciliary body was seen in the scleral wound. There was no bleeding from the ciliary body and no vitreous could be seen throughout the whole procedure. The scleral wound was sutured with interrupted 7–0 silk sutures. As the edges of the scleral wound were brought in apposition the presenting ciliary body was reposited with a thin iris spatula. The edges of the upper end of the scleral wound 9 mm from the limbus were treated with superficial diathermy. The medial rectus was re-attached to its insertion. The hyphaema was washed out through a keratome incision in the temporal corneal periphery. Evacuation of the hyphaema allowed visualization of a clear intact lens; in the postoperative period hyphaema filled one-third of the anterior chamber one week after the operation. The cornea remained clear throughout. The anterior chamber appeared to be of average depth. From 4.0 to 5.0 o'clock, remnants of iris could be seen. The lens was mostly clear with a layer of blood clot adherent to its posterior aspect in the lower nasal quadrant. Fundus details could not be clearly seen. Intraocular pressure was 8 mmHg by applanation tonometry. The eye was dressed daily with atropine drops and an antibiotic ointment; systemic corticosteroid treatment was started on the tenth postoperative day.



One month after the injury the visual acuity with pinhole correction was 6/18. The eye was quiet and the

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Address for reprints: Dr E. Aviel, Barzilai Medical Centre, Ashkelon, Israel cornea clear. There was no aqueous flare in the anterior chamber. The lens could now be seen to be subluxated medially. The taut zonules could be seen at the equator of the lens from 1.0 to 4.0 o'clock. Fundus details could now be visualized and there were no pathological findings, but the lower nasal quadrant could still not be seen as the blood remnants obscured the posterior aspect of the lens in this area.

On gonioscopy, in most of the nasal half, the angle structures were hidden by the equator of the subluxated lens. From 11.0 to 3.0 o'clock, ciliary processes stretched by the taut zonules could be seen. From 3.0 to 6.0 o'clock there was traumatic recession of the angle of the anterior chamber.

One year after the injury the visual acuity in the left eye is 6/6 with pinhole correction. The intraocular pressure is 15 mmHg by applanation tonometry. There is no change in the slit-lamp and fundoscopic findings.

Discussion

Sedan (1966) and Turut and others (1971) reported cases of traumatic cyclodialysis without corneoscleral wound. These cases could be described as traumatic recess of the angle of the anterior chamber. In Turut's two cases the hypotonia that appeared supports the view that there was a cyclodialysis cleft as a result of the injury. Duke-Elder (1972) described a case in which the ciliary body was completely torn from its anterior scleral attachment with backward displacement of the iris; there was a continuity between the anterior chamber and the suprachoroidal space. Such an injury may give the appearance of aniridia.

The case reported here differs in that the iris extruded from the scleral wound. There was no vitreous presentation and no haemorrhage from the wound. It is therefore assumed that the ciliary body remained intact in spite of the severe trauma. The sharp edge of the instrument produced the pathway for the iris prolapse after tearing most of it out from its root.

The final visual acuity of 6/6 is in keeping with the results of Trobe and Keeney (1974) who reported a final visual acuity of 20/25 in three cases of traumatic aniridia. In our case the intraocular pressure is still normal one year after the injury.

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Intracameral injection of gentamicin
Report of a case

MUHIB S. TARAKJI AND KHALID F. TABBARA
From the Department of Ophthalmology, American University of Beirut, Lebanon

Prompt and effective administration of antibiotics is of crucial importance in all cases of intraocular infections. Intraocular minimum inhibitory concentration of antibiotics is hardly achieved with antibiotics administered via the conventional routes (Furgiuele, 1967, 1970; Litwak, Pettit, and Johnson, 1969; Green and Leopold, 1965; Golden and Coppel, 1970). Recently Peyman, May, Ericson, and Apple (1974) found that 250 to 1000 μg of gentamicin could be injected into the anterior chamber of normal rabbits' eyes without damage to the cornea, lens, or retina. Peyman, Vastine, Cronch, and Herbst (1974) also reported treatment of five cases of bacterial endophthalmitis with intracameral and intravitreal injection of gentamicin and dexamethasone with good visual results.

A case of bacterial endophthalmitis in a patient who regained normal vision after intracameral and subconjunctival injections of gentamicin sulphate is presented.

Case report

A 25-year-old man was sent to hospital on 4 February 1975. For the previous five days he had had redness and pain in the left eye since being struck in that eye with a pointed splinter of wood. Vision was perception of light in the left eye (Fig. 1). The lids were swollen and the conjunctiva was chemotic. There was a paracentral corneal ulcer involving the deeper layers of the stroma. A small 1·0-mm pointed foreign body was stuck in the cornea with its tip projecting into the anterior chamber. There was a hypopyon filling one-third of the anterior chamber with 4+ cells. The pupil was mid-dilated and the iris adherent to the corneal ulcer at 9 o'clock. The lens appeared to be clear. Details of the vitreous and fundus could not be seen. Topical tetracaine 0·5 per cent was instilled into the conjunctival sac. The corneal foreign body was removed. A 25 gauge needle attached to 1-ml syringe was introduced into the anterior chamber at the limbus at 4 o'clock and 0·4 ml of aqueous was aspirated. Gram's stain of the aqueous revealed numerous polymorphonuclear neutrophil leucocytes and Gram-positive cocci. Cultures grew heavy growth of *Staphylococcus epidermides* coagulase negative. The organism was sensitive to gentamicin.

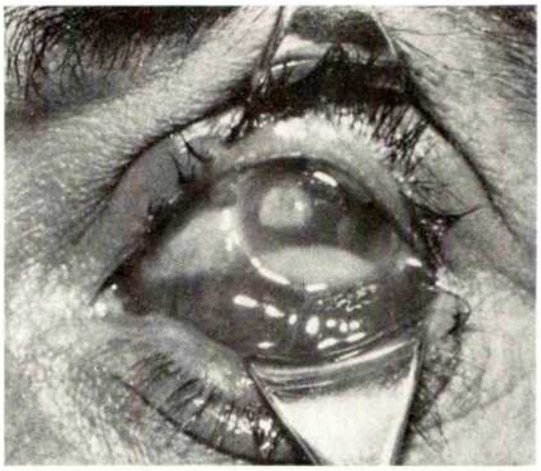

FIG. 1 *Site of penetrating injury in the cornea and evidence of endophthalmitis*

A total of 0·4 ml (200 μg) of gentamicin was injected into the anterior chamber through the same corneal tract; 40 mg of gentamicin were given subconjunctivally. The patient was then started on local 1 per cent atropine drops twice daily and gentamicin drops every hour.

In 48 hours there was marked clinical improvement, and the lid swelling and conjunctival chemosis had subsided. One week later the corneal ulcer had healed completely leaving an anterior iris adhesion. The central cornea and the lens were clear and there was no evidence of endothelial damage. The hypopyon had disappeared completely. Four weeks later the patient had a white left eye with a nasal anterior adherent leucoma and a visual acuity of 20/20 (Fig. 2).

Discussion

Intracameral and intravitreal injection of gentamicin may be considered as a useful and effective procedure in the treatment of bacterial endophthalmitis. Anterior chamber paracentesis provides

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Dr M. S. Tarakji is currently a research fellow at Albany Medical Center, Department of Ophthalmology, Albany, NY 12208, USA

Address for reprints: Dr M. S. Tarakji, Albany Medical Center, Department of Ophthalmology, Albany, NY 12208, USA

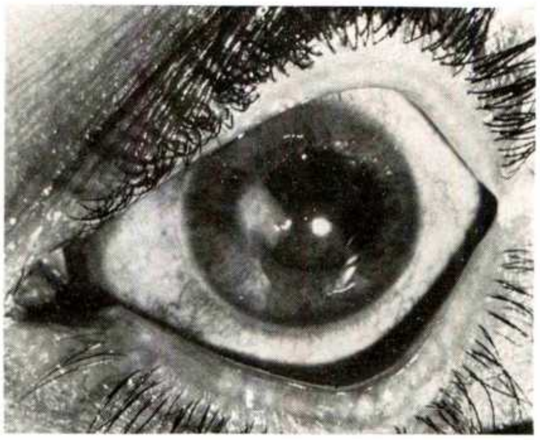

FIG. 2 *Eye of patient 4 weeks after treatment with intracameral and subconjunctival gentamicin*

the material for prompt identification of the offending organism (Allensmith, Skaggs, and Kimura, 1970). It also provides a means of delivering a high concentration of antibiotics into the anterior chamber without any untoward effects. This procedure can easily be performed in minor surgery without any special instrumentation. The intracameral and subconjunctival injections of gentamicin were effective in irradicating the infection and regaining normal vision without being clinically detectable and without the administration of systemic antibiotics.

Staphylococcus epidermidis coagulase negative, which was recovered from the present case, is usually regarded as a harmless organism. However, it has long been known to be a potential pathogen in cases of bacterial endocarditis in the presence of rheumatic valvular disease. Valenton, Burbaker, and Allen (1973) and Forster (1974) reported cases of endophthalmitis, mainly after cataract surgery from which *Staphylococcus epidermidis* coagulase negative was recovered. They emphasized the potential pathogenicity of this organism, the good response to antibiotics, and the good visual outcome.

Summary

A case of bacterial endophthalmitis secondary to a penetrating injury was successfully treated with intracameral topical and subconjunctival injections of gentamicin. After treatment the patient had normal vision and there was no evidence of toxic side-effects on the anterior segment of the eye including the endothelium, angle structures, and lens. The potential pathogenicity of *Staphylococcus epidermidis* is again emphasized.

We are grateful to Miss Eleonore Shweiry for her secretarial assistance.

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Vitrectomy in 125 eyes with diabetic vitreous haemorrhage

GHOLAM A. PEYMAN, MOTILAL RAICHAND, FELIPE U. HUAMONTE,
KRISHAN C. NAGPAL, MORTON F. GOLDBERG, AND DONALD R. SANDERS
From the Department of Ophthalmology, University of Illinois
Eye and Ear Infirmary, Chicago

Vitreous haemorrhage has been one of the main causes of blindness in the diabetic patient. Before the advent of the new automated vitrectomy instruments, there was no effective treatment for this condition. Caird, Burditt, and Draper (1968) reported that 31 per cent of diabetic patients were registered blind within one year after the onset of vitreous bleeding. This report documents the visual outcome and surgical and postoperative complications in 125 eyes with diabetic vitreous haemorrhage.

Methods

A total of 125 eyes of 119 consecutive diabetic patients with vitreous haemorrhage of longer than six months' duration underwent pars plana vitrectomy. Their preoperative visual acuities ranged from perception of light to 20/400. Sixty-seven eyes had simple diabetic vitreous haemorrhage, 48 eyes had tractional retinal detachment in addition to vitreous haemorrhage, and five eyes demonstrated rubeosis iridis and vitreous haemorrhage. Five eyes had all three conditions. All patients had proliferative diabetic retinopathy, which was known preoperatively or became evident upon clearing the haemorrhage. Preoperatively all patients underwent complete physical examination, with particular attention to their diabetic management, and a complete ocular examination with emphasis on visual acuity (including entoptic phenomenon, 2-point discrimination and light projection in those patients with less visual acuity than hand movements), presence of rubeosis iridis, applanation tensions, and presence of lenticular opacities.

In cases with vitreous opacification precluding adequate fundus examination, ultrasonography and, in selected cases, bright-flash electroretinography were performed.

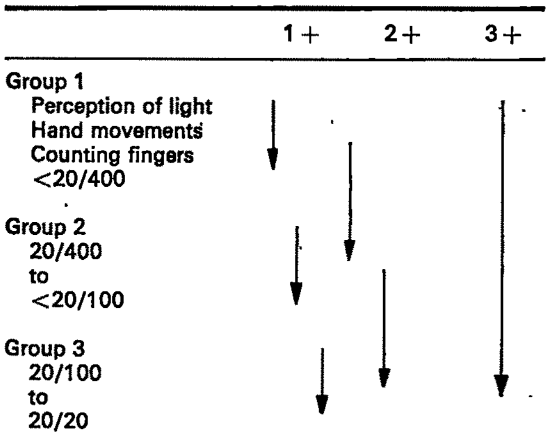
The surgical techniques and instrumentation have been described previously (Peyman, Huamonte, and Goldberg, 1975; Peyman and Sanders, 1975). In more than 95 per cent of cases these were performed under local anaesthesia; their follow-up period ranged from six months to two years. In all cases the operative notes and operative complications were recorded by the operative assistant, and the data were collected by two independent observers (MR and KN).

Results

VISUAL ACUITY

Visual outcome has been assessed by the Peyman-Sanders' classification of visual improvement after vitrectomy (Figure) (Table I) (Peyman and Sanders, 1975; Peyman, Huamonte, and Goldberg, 1976). Those eyes with simple vitreous haemorrhage had the most favourable visual outcome; 72 per cent had some visual improvement. The five eyes that had vitreous haemorrhage with tractional retinal detachment and rubeosis iridis did poorly with none showing improvement and two with worsened visual acuity.

Table II summarizes visual outcome based on the type of procedure performed.



1+ = Improvement within any group
2+ = Improvement to the next better group
3+ = Improvement from Group 2 to Group 3

FIGURE *Visual improvement after vitrectomy*

Address for reprints: Gholam A. Peyman, MD, University of Illinois Eye and Ear Infirmary, 1855 W. Taylor Street, Chicago, Illinois 60612, USA

Table I *Diagnoses and improvement in visual acuity*

Diagnoses	*No. of eyes*	*Improvement in visual acuity**				
		3+	2+	1+	*Same*	*Worse*
Vitreous haemorrhage	67	6 (9)	14 (21)	28 (42)	14 (21)	5 (7)
Vitreous haemorrhage, tractional retinal detachment	48	2 (4)	8 (17)	23 (48)	10 (21)	5 (10)
Vitreous haemorrhage, rubeosis iridis	5	2 (40)	0	0	3 (60)	0
Vitreous haemorrhage, tractional retinal detachment, rubeosis iridis	5	0	0	0	3 (60)	2 (40)
Total	125	10 (8)	22 (17)	51 (41)	30 (24)	12 (10)

*Peyman-Sanders' classification (1975)
Percentages are given in parentheses

Table II *Surgical procedure and improvement in visual acuity*

Surgical procedure	*No. of eyes*	*Improvement in visual acuity**				
		3+	2+	1+	*Same*	*Worse*
Pars plana vitrectomy	55	4 (7)	10 (18)	17 (31)	18 (33)	6 (11)
Pars plana vitrectomy and pars plana lensectomy	54	6 (11)	9 (17)	25 (46)	11 (20)	3 (6)
Clear corneal lens extraction, and pars plana vitrectomy	16	0	3 (19)	9 (56)	2 (12)	2 (12)
Total	125	10 (8)	22 (17)	51 (41)	31 (25)	11 (9)

*Peyman-Saunders' classification (1975)
Percentages are given in parentheses

OPERATIVE AND POSTOPERATIVE COMPLICATIONS

Table III itemizes the complications encountered in these eyes grouped according to whether tractional detachment and rubeosis iridis were present.

The major operative complication was bleeding from iris vessels and intravitreal fibrovascular stalks, which stopped by increasing the intraocular pressure or, rarely, by using intraocular diathermy. Two small retinal tears produced with the vitrophage were adequately treated with cryocoagulation and a buckling procedure. No retinal dialysis occurred.

The most common early postoperative complication was corneal haze or striate keratopathy (71 per cent) which cleared in most cases. Thirty per cent of cases demonstrated a transient increase in intraocular pressure. One case of bacterial endophthalmitis occurred when the operating room personnel neglected to add 4 µg/ml of gentamicin to the vitrectomy infusion fluid, which is our standard prophylaxis. This eye subsequently required evisceration (May and Peyman, 1976).

The most common late complications after vitrectomy were persistent corneal oedema (11 per cent), repeated vitreous haemorrhage (13 per cent), and hyphaema (9 per cent). Six per cent of eyes had a persistent increase in intraocular pressure refractory to medical and surgical management at the time of last examination. Seven of eight eyes with clear lenses before vitrectomy developed posterior subcapsular cataracts sufficient to impair vision significantly. The rest of the patients in this series were aphakic after pars plana surgery. Five per cent of patients developed rubeosis iridis not noted preoperatively, and 3 per cent developed phthisis bulbi. In two cases, rhegmatogenous retinal detachment developed with holes thought to be unrelated to vitreous surgery, and in four cases preexisting tractional detachments worsened without evidence of hole formation.

Discussion

In our series, all patients undergoing vitrectomy met the criteria for their being registered as blind. After surgery, 25 per cent no longer were blind. An additional 40 per cent were improved, allowing most of them to function in familiar surroundings.

The major intraoperative and postoperative complication was bleeding related to neovascular tissue. Significant surgical complications related to intraocular manipulation such as retinal dialysis were notably absent. Postoperative transient and persistent corneal disorders may in part reflect the sensitivity of diabetic tissue to surgical trauma or inflammation.

We consider the complication rate acceptably low for the degree of improvement in visual acuity obtained and in view of the untreated natural course of this disease.

Summary

A total of 125 consecutive eyes, all registered blind with diabetic vitreous haemorrhage, underwent pars plana vitrectomy with the vitrophage. Sixty-six per cent experienced some improvement in their visual acuity; 24 per cent were unchanged and 10 per cent were worse postoperatively. The major surgical complication was controllable haemorrhage (23 per cent). No retinal dialysis occurred. Significant

Table III *Complications*

Complication	*Total*	*Diagnoses*			
		Vitreous haemorrhage	*Vitreous haemorrhage, tractional retinal detachment*	*Vitreous haemorrhage, rubeosis iridis*	*Vitreous haemorrhage, tractional retinal detachment, rubeosis iridis*
No. of eyes	125	67	48	5	5
with complications	109 (87)	57 (85)	42 (88)	5 (100)	5 (100)
Surgical					
Bleeding with spontaneous clearing	23 (18)	9 (13)	10 (21)	2 (40)	2 (40)
Bleeding with clearing after lavage or diathermy	6 (5)	2 (3)	4 (8)	0	0
Retinal tears	2 (2)	1 (1)	1 (2)	0	0
Lens particles in vitreous	5 (4)	2 (3)	3 (6)	0	0
Early postoperative (within 2 weeks)					
Transient corneal oedema/striae	89 (71)	52 (78)	27 (56)	5 (100)	5 (100)
Transient rise in intraocular pressure	38 (30)	20 (30)	10 (20)	4 (80)	4 (80)
Repeated vitreous haemorrhage	10 (8)	4 (6)	5 (10)	1 (20)	0
Hyphaema	8 (6)	6 (9)	1 (2)	0	1 (20)
Endophthalmitis	1 (1)	1 (1)	0	0	0
Haemolytic glaucoma	10 (8)	7 (10)	0	2 (40)	1 (20)
Late postoperative (after 2 weeks)					
Persistent corneal oedema/bullous keratopathy	14 (11)	10 (15)	4 (8)	0	0
Persistent rise in intraocular pressure	8 (6)	3 (4)	4 (8)	1 (20)	0
Repeated vitreous haemorrhage	16 (13)	9 (13)	7 (14)	0	0
Hyphaema	11 (9)	4 (6)	5 (10)	0	2 (40)
Cataract	7 (6)	5 (7)	2 (4)	0	0
Rubeosis iridis	6 (5)	4 (6)	2 (4)	0	0
Phthisis bulbi	4 (3)	0	2 (4)	0	2 (40)
Retinal detachment	6 (5)	2 (3)	3 (6)	0	1 (20)

Percentages are given in parentheses

postoperative complications were transient (71 per cent) and persistent (11 per cent) corneal oedema, early (8 per cent) and late (13 per cent) vitreous haemorrhage, transient (30 per cent) and persistent (6 per cent) rise in intraocular pressure, and rubeosis iridis (5 per cent).

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Management of persistent hyperplastic primary vitreous by pars plana vitrectomy

GHOLAM A. PEYMAN, DONALD R. SANDERS, AND KRISHAN C. NAGPAL
From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago, Illinois

In the past the surgical treatment of persistent hyperplastic primary vitreous (PHPV) has been mainly carried out via an anterior segment approach. With the newly developed vitreous cutting and aspirating instruments, pars plana vitrectomy may be a workable surgical alternative (Smith and Maumenee, 1974; Michels, Machemer, and Mueller-Jensen, 1975; Peyman and Sanders, 1975).

We describe two cases of PHPV handled by pars plana surgery.

Patients

CASE 1

A 3-month-old Black boy was noted to have leucocoria in the right eye at two months of age. Prenatal and developmental histories were unremarkable. There was no family history of ocular abnormalities. Physical examination showed only an easily reducible right inguinal hernia.

The child's left eye was normal, with corneal diameter of 11·5 × 11·5 mm. He had a deviation in the right eye with a constant 24 degrees of right esotropia. The right eye was normal externally with a corneal diameter of 11 × 11 mm. Intraocular pressure by Schiötz tonometry was 24 mmHg in the left eye and 21 mmHg in the right. Gonioscopy showed normal angles in both eyes. A posterior polar cataract in the right eye spared the periphery of the lens, through which was visible a large fibrovascular stalk (Fig. 1) with prominent vessels emanating from the optic disc. Surrounding the base of the stalk was a localized central tractional retinal detachment. There was no evidence of elongated ciliary processes at the periphery of the lens.

Address for reprints: Gholam A. Peyman, MD, University of Illinois Eye and Ear Infirmary, 1855 W. Taylor Street, Chicago, Illinois 60612, USA

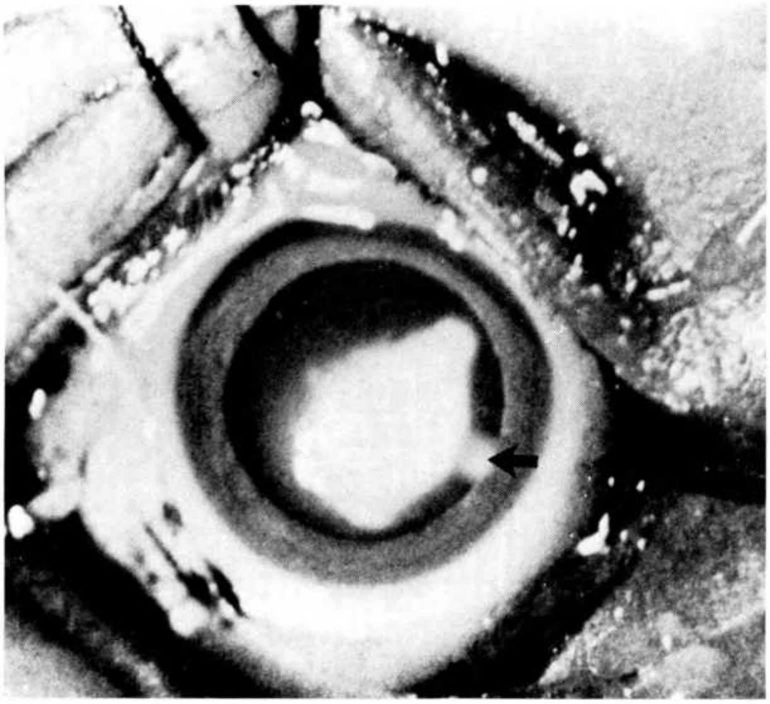

FIG. 1. *Preoperative appearance of patient's right eye demonstrating cataract and intravitreal fibrovascular stalk (arrow)*

Surgical technique

Under general anaesthesia with four 4–0 silk bridle sutures under the rectus muscles, a no. 15 Bard-Parker blade cut a 3·5 mm long limbus-parallel sclerotomy down to the choroid, 2·5 mm posterior to the corneoscleral limbus in the inferotemporal quadrant. The ends of a 5–0 Dexon mattress suture, placed through the sclerotomy lips, were tied loosely. Toothed forceps grasping the sclerotomy lips stabilized the eye while a radiofrequency diathermy probe (Peyman and Dodich, 1972), inserted through the sclerotomy, coagulated the large vessels of the intravitreal stalk without complication. A no. 52S Beaver blade inserted into the equator of the lens created a track through the sclerotomy for the vitrectomy instrument. The lens fragmenter unit (Peyman, Huamonte, and Goldberg, 1975) of the vitrophage broke up the lens, which was removed together with the posterior polar cataractous plaque and the anterior portion of the fibrovascular stalk, with the wide-angle cutting unit of the vitrophage (Peyman, 1976). An anterior vitrectomy was performed with the same unit. The vitrophage was removed, and the 5–0 Dexon mattress suture was tied and reinforced centrally with an interrupted suture of 5–0 Dexon. Sutures of 5–0 catgut closed the peritomy, and the eye received atropine and an antibiotic corticosteroid preparation topically.

Two weeks after operation the eye was quiet, and only a slight vitreous haze clouded the media (Fig. 2). The stump of the fibrovascular stalk appeared retracted, and the tractional retinal detachment was somewhat flattened. Ocular examination has remained unchanged after being followed-up for six months.

CASE 2

A 4-month-old White boy was noted to have leucocoria in the left eye at approximately six weeks of age. Prenatal and developmental histories were noncontributory. At three months of age the child was noted to have, in the left eye, a small cornea, shallow anterior chamber, small cataractous lens, and a white retrolental mass with elongated ciliary processes nasally. Intraocular pressure (Schiötz) was 17 mmHg and the fundus could not be visualized. *X*-ray films of the orbit revealed no intraocular calcifications, and ultrasonography revealed a slightly microphthalmic eye with a thickening at the posterior lens capsule. The patient was then referred to us for treatment.

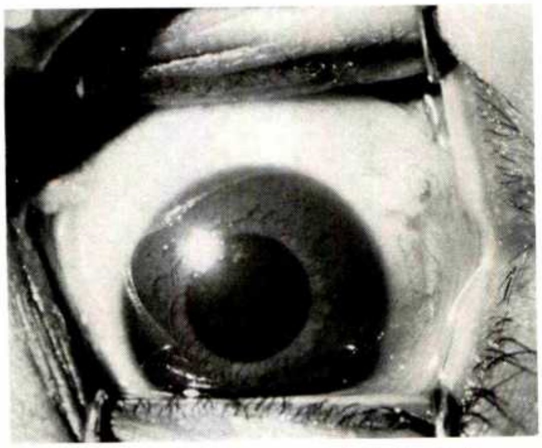

FIG. 2 *Appearance of eye 10 days postoperatively demonstrating clear pupillary opening with no evidence of ocular inflammation*

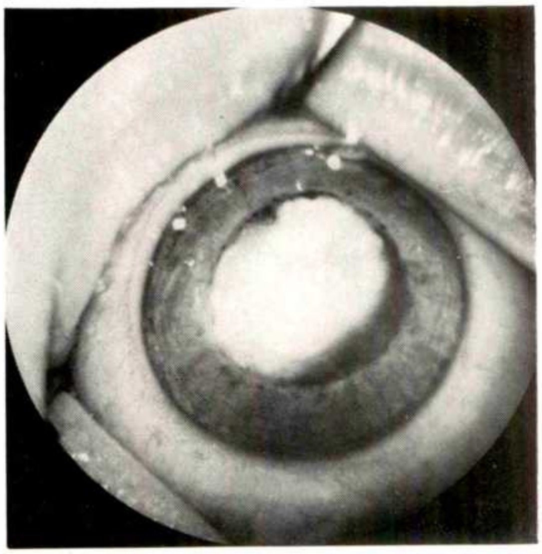

FIG. 3 *Preoperative view demonstrating cataractous lens*

The child's right eye was normal with corneal diameters of 11 × 11·5 mm. There was unsteady fixation in the left eye with a variable deviation. The left eye appeared microphthalmic with corneal diameters of 10·25 × 10·25 mm. Intraocular pressure (Schiötz) was 17 mmHg (4/5·5). A distinct dense pupillary membrane extended from collarette to collarette; in addition, an intact tunica vasculosa lentis and a retrolental mass extended into the lens (Fig. 3). A red reflex could be elicited temporally around the retrolental mass. The operative procedure was identical to that in Case 1 except that the intravitreal stalk was not diathermized. There were no operative or postoperative complications and on the first postoperative day the conjunctiva was mildly hyperaemic, the cornea was clear, and retinal fundus detail could be seen with a hand-light. At two weeks postoperatively only mild conjunctival hyperaemia was noted (Fig. 4), and at examination three months postoperatively there was no evidence of inflammation, the ocular media were clear, and the retina was normal (Fig. 5).

Discussion

Most surgical approaches to the treatment of PHPV have been via an anterior segment approach (Collins, 1908; Wolfe, 1954; Reese, 1955; Acers and Costen, 1967; Gass, 1970; Smith and

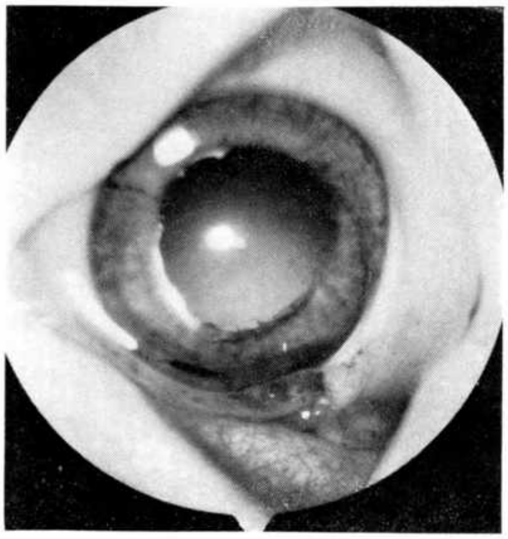

FIG. 4 *Postoperative view demonstrating wide and clear pupillary opening*

Maumenee, 1974); either a discission or excision of the retrolenticular tissue through a large corneoscleral limbal incision followed an aspiration procedure. Nevertheless, this large incision provides poor operative exposure for removal of retropupillary tissue.

Michels and Ryan (1975) reported two cases of PHPV among 100 vitrectomy cases although the operative technique and postoperative results were not specified. Michels and others (1975) have said that they prefer to use an incision at the limbus rather than at the pars plana in these microphthalmic eyes. We advocate early surgical intervention in these cases before complications such as bleeding into the lens or vitreous or traction on the ciliary body occurs or becomes worse. With development of the cataract, a lens-induced flat anterior chamber and secondary glaucoma may develop. Although the visual prognosis in these cases is poor because of macular aplasia, tractional detachments and deprivation amblyopia, removal of the anteroposterior traction caused by the hyperplastic primary vitreous allows the eye to grow and to achieve reasonable cosmesis.

Summary

Two children with persistent hyperplastic primary vitreous (PHPV) underwent vitrectomy and lensectomy via the pars plana to remove the fibrovascular stalk. Postoperatively the eyes were quiet, only a slight vitreous haze obscured the fundus view in the immediate postoperative period, and the stumps of the stalks retracted. Early surgical treatment of PHPV may prevent later serious complications.

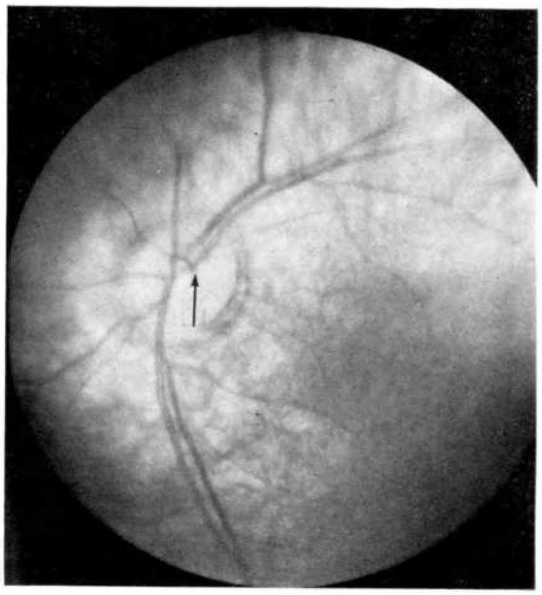

FIG. 5 *Fundus view: note clarity of the media. Arrow indicates retracted vascular stalk*

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Lens extraction with ultrasound
Experiments in rabbits

DOUGLAS McG. CLARKSON*
Departments of Medical Physics and Ophthalmology
AND
CALBERT I. PHILLIPS
Department of Ophthalmology, University of Edinburgh and Princess Alexandra Eye Pavilion, Royal Infirmary, Edinburgh

As a step in the development of a system for the removal of hard cataracts in humans using ultrasonic vibrations, a prototype device has been used to extract the (normal) rabbit lens.

Various methods of using ultrasonic vibrations for cataract extraction have been reported (Kelman, 1969; Girard and Hawkins, 1974; Kuwahara, 1970). An essential feature of the procedure is the insertion into the anterior chamber of a small vibrating needle at the tip of which lens fragmentation occurs.

Method

IRRIGATION-ASPIRATION SYSTEM

General description

The hollow needle portion of the aspirator-fragmentor (22 G) is inserted into the anterior chamber at the limbus temporally through a self-sealing incision. Inclined to this first needle at about 90 to 100°, a 25 G standard disposable syringe needle is similarly inserted at the limbus at around 6 o'clock (Fig. 1). Each needle is connected with a push-pull machine (Phillips and Wang, 1971) by 150 cm lengths of Portex manometer tubing: 'disposable manometer line', luer fitting, length 150 cm, type 200/490/150.† The push-pull machine allows the simultaneous irrigation of fresh saline into the anterior chamber and aspiration of saline along with lens fragments at equal rates. Two 50-ml Plastipak syringes, the plungers of which are secured in fixed brackets, lie on either side of a central threaded rod facing in opposite directions. Rotation of the rod moves the common transverse piece which grips the barrels of the syringes (Fig. 2). The motion of the syringe barrels relative to their respective plungers is therefore equal but in opposite directions. This equalizes the irrigation and aspiration flows because the cross-sectional areas of the syringes are identical. The grips for the plungers allow independent control of the syringe volumes when required so that an adequate depth of anterior chamber can be maintained if leakage occurs at entry points of the needles.

Preliminary settings

Initially the irrigation syringe with attached manometer tubing is filled with about 55 ml of saline. Trapped air bubbles are expelled and the syringe with attached tubing is fixed to the irrigation arm of the push-pull machine with the associated plunger control set for maximum independent fluid input (about 55 ml). The aspiration syringe and attached manometer tubing are filled only to the extent required to eliminate air bubbles; with a small amount in the syringe the tubing is then fitted into the aspiration arm of the push-pull machine where the plunger control is used to expel most of the residual contents of the syringe.

The elimination of air bubbles from the irrigation limb prevents their entering the anterior chamber to obscure the operator's view. Also, in both the

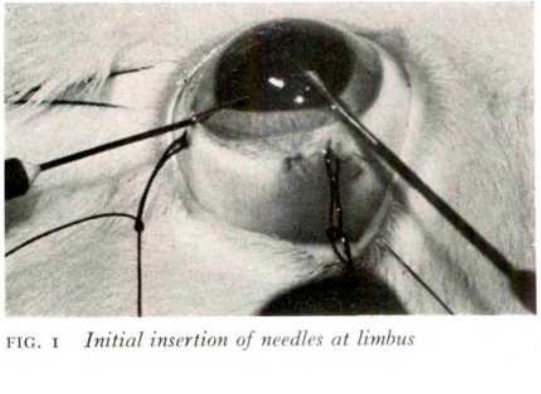

FIG. 1 *Initial insertion of needles at limbus*

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*Present address: Respiratory Laboratory, City Hospital, Greenbank Drive, Edinburgh EH10 5SB

†Portex Ltd, Hythe, Kent.

Address for reprints: Professor C. I. Phillips, Department of Ophthalmology, Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA

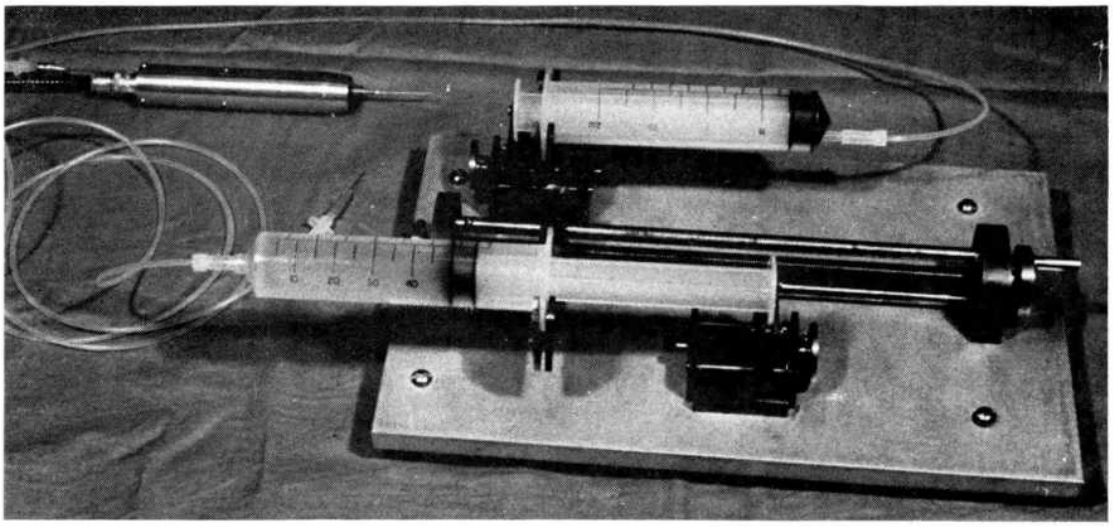

FIG. 2 *Push-pull machine at initial settings with mounted syringes to which are attached the irrigation and aspiration needle and tubing combinations*

irrigation and the aspiration limbs careful elimination of air bubbles ensures that the associated positive and negative pressures are maintained at optimum values. The negative pressure at the aspirator-fragmentor needle aids fragmentation of the lens.

THE LENS FRAGMENTOR/ASPIRATOR

The lens aspirator/fragmentor (Clarkson and Phillips, 1975) employed in these experiments (Fig. 3) comprises two main parts:

the outer case with associated power socket

the vibrator which undergoes longitudinal vibrations.

The device is powered by an oscillating signal from an electrical generator at a specific resonant frequency of the vibrational assembly. Piezoelectric crystals* are alternately expanded and compressed (mainly longitudinally) by the voltage signal and in so doing supply vibrational energy to the vibrator assembly. This vibrator is specifically designed to produce *a significantly greater amplitude of vibration at the active tip of the instrument compared with that at other points along its axis,* a result which is achieved by using an 'acoustic horn' (Eisner, 1967; Merkulov, 1957; Merkulov and Kharitonov, 1959; Neppiras, 1963). It is at the active tip that lens material can be fragmented.

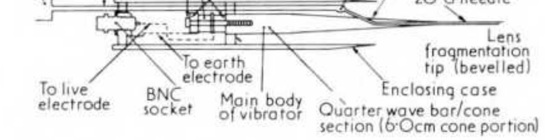
Leur lock head
Cap screw compression bolt
Solder joint
Angled side exit
Large bore aspiration needle
Piezo electric crystals
Backing bar
22 G, 21 G or thin walled 20 G needle
Lens fragmentation tip (bevelled)
To earth electrode
To live electrode
BNC socket
Main body of vibrator
Enclosing case
Quarter wave bar/cone section (6·0cm cone portion)

FIG. 3 *Section along the ultrasonic lens fragmentor, showing the passive case, power input socket, and assemblies for luer aspiration. Also shown is the active vibrator element extending along the central axis between the lens fragmentation tip and the cap screw compression bolt. Vibrator is encased by an outer metal case*

This active tip is at the bevelled end of a 3 cm length of stainless steel tubing, typically of 22 G or 21 G specification (less than 1 mm outside diameter). This tubing, through which fragmented lens matter is sucked, exits from the side of a cone portion of the vibrator, where it is soldered (Magna type) to a larger-diameter stainless steel tube. This tube runs parallel with the axis of the vibrator inside the case towards the face of the power socket. From there it protrudes about 4 cm where it terminates in a luer lock attachment. To that attachment is connected the disposable manometer tubing.

THE ELECTRICAL GENERATOR

General description

The electrical generator shown schematically in Fig. 4 delivers to the vibrator a sinusoidally varying voltage signal which can be altered both in frequency and amplitude, permitting optimum tuning of the mechanical vibrator and control of amplitude

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*Vernitorn Ltd, Thorn Hill, Southampton

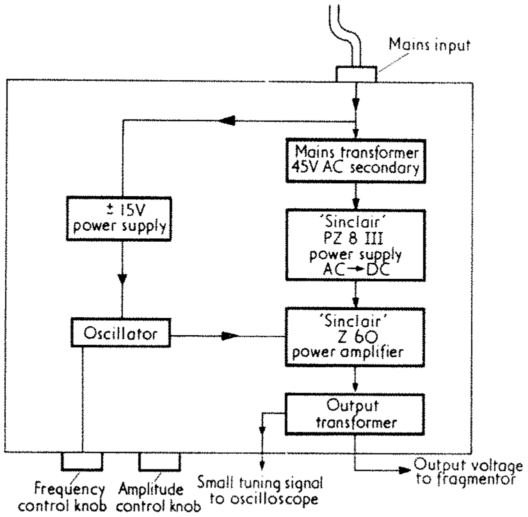
Mains input
Mains transformer 45V AC secondary
± 15V power supply
'Sinclair' PZ 8 III power supply AC→DC
Oscillator
'Sinclair' Z 60 power amplifier
Output transformer
Frequency control knob
Amplitude control knob
Small tuning signal to oscilloscope
Output voltage to fragmentor

FIG. 4 *Simplified block diagram of electrical generator. The generator draws power from the mains supply and delivers an output signal of varying frequency and amplitude to the lens fragmentor*

of vibration at the active needle tip. Of the two frequency ranges available, the lower one which extends from about 25 to 45 kHz is employed. The voltage output is continuously variable between 0 and 125 V root mean square.

Mode of operation

An oscillator (Wein bridge type) inputs a signal of controllable frequency and amplitude to the power amplifier. The output of this amplifier is some 50 times greater and this is further increased by a factor of 10 with an output transformer, making available to the crystal elements in the vibrator an oscillating voltage of sufficient amplitude to produce the necessary active vibration at the tip of the needle. At the resonant frequency of the vibrator, the current drawn from the generator is at a local maximum, and a voltage signal proportional to the generator current is observed on an oscilloscope in order to monitor this resonance. The oscillator draws power from a ±15 V power supply while the amplifier is powered from a source delivering 45 V DC. This in turn is supplied with 45 V AC from the secondary windings of a mains transformer. The generator draws no more than about 7 W from the mains under normal operating conditions; of these about 2 W at most will be supplied to the fragmentor itself.

IN VIVO RABBIT LENS EXTRACTION

To date, eight experiments on rabbits have been done, two with survival.

Preliminary

Atropine was administered topically at five-minute intervals beginning 30 minutes before the start of the procedure, while an intravenous injection of nembutal given in conjunction with an ether mask was used to produce a sufficiently deep state of anaesthesia. Phenylephrine 10 per cent and cocaine hydrochloride 4 per cent were administered once, five minutes before the operation. (Some deaths early in the anaesthetic were probably due to systemic absorption of too frequently administered phenylephrine 10 per cent, cocaine 4 per cent, or atropine 1 per cent.) Lid sutures were used. Two limbal traction sutures were inserted, one temporally and one at 6 o'clock, to allow firm fixation of the eyeball so that accurate incisions of half-thickness of cornea just anterior to the limbus could be made.

Needle insertion and anterior capsule incision

Against countertraction on the limbal fixation sutures, the needle-fragmentor and the irrigation needles were easily inserted through the deeper half of the cornea. The bevel at the fragmenting tip must be sufficiently sharp to allow penetration with minimal corneal trauma. The resulting punctures should be small enough to minimize loss of aqueous humour during and after the operation. The irrigation needle and the aspirator-fragmentor needle, which are reasonably manoeuvrable in the anterior chamber, are used to incise the anterior lens capsule in a cruciate pattern.

Lens fragmentation and aspiration

The process of lens removal is initiated by passing saline through the eye at a rate of about 2 ml a minute and then switching on power to the tuned lens fragmentor. Typically 1·5 W of electrical power at a root mean square voltage of 120 V is supplied at an oscillating frequency of about 35 kHz.

Lens material sucked on to the active tip is 'shredded' by the ultrasonic vibrations, and drawn down the suction pathway of the lens fragmentor-aspirator into the collecting syringe. In the absence of ultrasonic vibrations, however, no lens cutting is achieved.

The aspiration flow serves also to stabilize the temperature of the fragmentor which tends to heat up because of mechanical losses in the metal which experiences large cyclic stressing forces. To avoid over-heating, power must be cut off when aspiration flow ceases and not turned on again until aspiration flow is re-established.

The lens material tends to prolapse into the anterior chamber and becomes more accessible, hence improving the cutting rate. Material can be scavenged from beneath the iris by aspiration in the absence of fragmentation while any leakage at the limbal incisions can be replaced by the use of the independent plunger control in the irrigation limb. All visible lens fragments with the exception of the posterior capsule and peripheral parts of the anterior capsule were generally removed in about 12 minutes, during which time about 25 ml of fluid had been used. Flow (and power) should be intermittent, otherwise the saline passes directly from the irrigator to the aspirator and avoids lens matter; during pauses in the flow of fluid, the tip of the aspirator-fragmentor should be positioned on lumps of lens matter which can then be scavenged and pulverized as soon as flow starts again. The fragmentor needle is then withdrawn. The anterior chamber is deepened by injection of saline through the irrigation needle which is also then withdrawn. On account of the small size of limbal wounds, there is usually no subsequent loss of anterior chamber and no need for suturing.

SUBSEQUENT OBSERVATIONS

Terminal experiments

In several experiments at the end of which the rabbit was killed, the condition of the vitreous face was assessed directly after the extraction procedure. It was generally found that the ruptured anterior capsule was inconspicuous. An intact posterior capsule always remained so that there was no loss of vitreous, although all lens material had been removed. There seemed to be no danger of vitreous aspiration, presumably because the irrigating fluid tends to go directly from the irrigation to the aspiration needle.

Survival experiments

Ethylene oxide gas has proved an effective agent for sterilizing the lens fragmentor. Any traumatized region at the limbus caused initially by a relatively forceful entry of the aspiration needle into the anterior chamber steadily decreases in extent until after three weeks only a small greyish opacity about 1 to 1·5 mm in diameter remains (Fig. 5). With care the needles can be inserted at right-angles to the surface of the cornea, and trauma can be minimized; if the tip of the needle is pointing even slightly towards the apex of the cornea, a rather long intracorneal track results with a larger area of traumatized cornea. With appropriate initial penetration, however, no such opacity was observed, initially or subsequently, which would seem to imply that the contact between the needle vibrating along its long axis and cornea does not, at the levels of vibration being used and with sufficient aspiration flow, contribute towards corneal opacity.

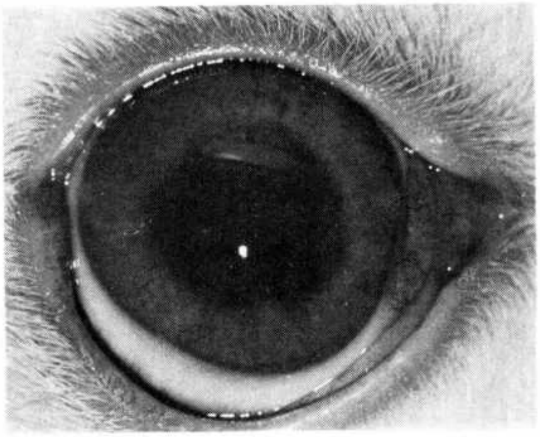

FIG. 5 *Corneal opacity at 12 o'clock (over pupil margin) —that is, at entry point caused by passage of aspiration needle along layers of cornea before entering anterior chamber*

TEMPERATURE STUDIES OF VIBRATING ASPIRATION NEEDLE

An experiment was done to measure the temperature variation of points along the powered vibrator while aspiration was carried out at carefully controlled rates using an infusion pump. A thermister (type STC U14) of about 0·5 mm diameter was carefully encapsulated using only sufficient epoxy resin to insulate it electrically from, and ensure excellent thermal contact with, the metallic surface of the vibrator. The thermister was wired in series with a 400 mV DC voltage source and a resistor of value similar to that of the thermister at room temperature. In the range of temperatures investigated (15 to 60°C) the voltage across the constant value resistor increased linearly with the thermister temperature, and in subsequent measurements an electrocardiogram chart recorder was used to measure the variation of this voltage with time.

General observations

Significant heating of the vibrator is produced only in the region between the needle tip and side exit of the aspiration duct on the cone portion. The heating is caused by mechanical losses in the structure which is undergoing large stressing forces. Equalization of temperatures occurs along the needle itself owing to thermal conduction and the temperature from apex to base of the cone portion falls because heat is conducted to regions where less is produced because stress forces are smaller. Important factors in determining the needle temperature are the input power and the rate of aspiration; however, overall design, especially the size of needle used, as well as the degree of acoustic coupling between the cone and needle sections, are also relevant.

Results

The excess temperature of the outer surface of the needle at the cone-needle junction for two different fragmentors at various aspiration rates is shown in Fig. 6. The 22 G needle fragmentor was powered at 1·0 and 1·9 W and compared with a 21 G needle fragmentor powered at 1·2 W. Significant heating would seem to occur only at the higher input powers for aspiration rates of less than 1 ml/min. For a given input power the 21 G needle, with its slightly larger annular area, tends to heat up more readily compared with the 22 G needle.

Fig. 7 shows the variation in thermister temperature. A steady aspiration only is first established. This is followed by a period of combined aspiration and power which in turn is followed by a period of power with no aspiration. The aspiration is then resumed, and finally the power is switched off. The fast response of the system is indicated by the rapid changes in temperature at the various steps.

Provided therefore, that the aspiration rate is, maintained at a level of at least 1 ml/min, there should occur no thermally induced corneal trauma. The Kelman probe (Kelman, 1969, 1973, 1974) differs somewhat in its thermal properties (Benolken, Emery, and Landis, 1974) in that irrigating fluid flows over the vibrating probe before it enters the anterior chamber. This may tend to increase the heat input into the anterior chamber compared with the independent irrigation-aspiration design.

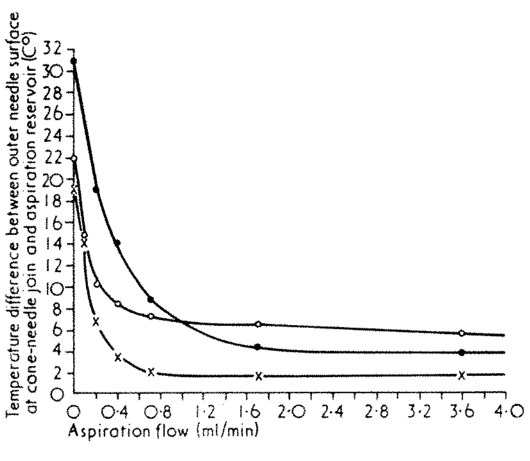

FIG. 6 *Graphs indicate measured rise in temperature of outer surface of 21 G and 22 G needle fragmentor at various aspiration rates together with power inputs, with the thermister in contact with the fragmentor at the cone-needle join*

○ 21 G needle probe at 1·2 W input
× 22 G needle probe at 1·0 W input
● 22 G needle probe at 1·9 W input

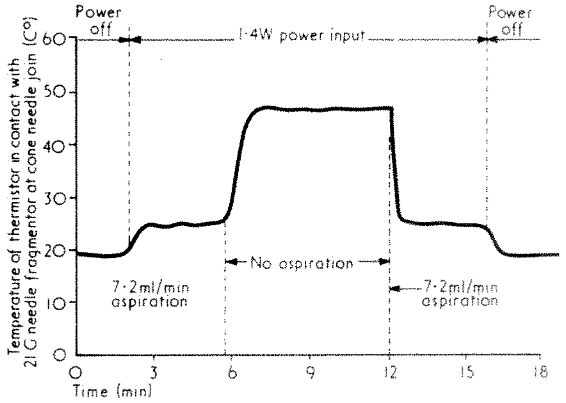

FIG. 7 *Typical thermister temperature/time variation initially with aspiration only (bottom left portion) then subsequent input of 1·4 W of electrical energy and later stoppage of aspiration. Aspiration is then resumed and power is later switched off*

ADVANTAGES OF PROCEDURE

Manoeuvrability of the cutting needle in the eye is enhanced because of its small outer diameter (an angle of about 135° can be swept out).

Also associated with size is increased access to eye which simplifies for example scavenging under the iris.

The limbal wounds do not usually require suturing.

PROPOSED USE IN HUMANS

It is intended, in the first place, to extract soft cataracts in humans using the general procedures outlined above—that is, to extract the lens material using small needles through an aperture in the anterior capsule. A new improved instrument is being constructed.

Capsule consideration: human capsule fragmentation studies in vitro

Even with a maximum tip amplitude of about 0·06 mm peak to peak excursion, no significant ultrasonically-induced breakdown of human capsule has so far been observed. This is in contrast with the softer rabbit capsule. The fronds of human capsule must not be allowed, however, to block the aspiration needle, which is an occurrence usually caused by the capsule impaling itself on the needle tip. Aspiration of capsule is facilitated by use of large-bore needles and well-developed bevelled needle tips. These features will encourage the capsule to be drawn into the aspiration duct rather than becoming lodged at the needle tip.

The capsule behaves in effect like a thin, tough polythene sheet which because of its small overall volume, can be drawn along the aspiration duct. Flaps of capsule 3 × 7 mm may be aspirated successfully by a needle of inner bore corresponding to a 20 gauge needle.

Procurement of suitable needles

While the use of larger-bore needles would ordinarily imply the disadvantage of decreased manoeuvrability and increased wound size, a process of electrolytic erosion may be employed by the manufacturer* to produce economically a needle of a given bore yet with any required thickness of wall. In this process, metal is evenly removed at a controlled rate from the outer surface of the needle while the inner diameter of the needle is unchanged.

It is also intended to use syringes of up to 100 ml capacity† in order to increase reserves of fluid in the irrigation/aspiration system.

Summary

The extraction of the rabbit lens is described using a 25 G irrigating needle and a 22 G aspirating needle; at the latter's bevelled tip lens fragmentation occurs due to the longitudinal ultrasonic vibrations generated there—an 'acoustic horn' causes the tip to vibrate with large amplitudes. The use of small needles allows considerable manoeuvrability in the anterior chamber and usually eliminates the need for corneal suturing. Push-pull coupled syringes equate the volume of irrigation with that of aspiration. This procedure makes possible lens extraction through an aperture in the anterior capsule of the rabbit's lens and a similar machine is being constructed for trial on human cataract.

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*Cooper's needle works, 261–265 Aston Lane, Birmingham B20 3HS

†Everett Medical Products Ltd, Mitcham, Surrey

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Perifoveal vascular leakage and macular oedema after intracapsular cataract extraction

TRAVIS A. MEREDITH, KENNETH R. KENYON, LAWRENCE J. SINGERMAN, AND STUART L. FINE
From the Wilmer Ophthalmological Institute, Baltimore, Maryland

Cystoid macular oedema is now a commonly recognized complication after cataract extraction. Irvine (1953) described a syndrome of spontaneous rupture of the anterior hyaloid face with vitreous adhesions to the wound, irritability of the eye, and reduction of vision secondary to macular changes. Gass and Norton (1966) correlated the typical ophthalmoscopic appearance of dilated spaces in the central macula with late pooling of fluorescein dye in these spaces after intravenous injection. Gass and Norton (1969) described the clinical course of the syndrome in a referral population of 48 patients. Typically, visual acuity was initially good and then declined 4 to 12 weeks after cataract extraction. Forty per cent of those eyes had the vitreous attached to the posterior surface of the wound and many eyes had inflammatory cells in the posterior vitreous. Other authors have reported that this syndrome occurs in approximately 5 to 7 per cent of patients after cataract extraction (Gehring, 1968; Maumenee and Meredith, 1974).

Irvine, Bresky, Crowder, Forster, Hunter, and Kulvin (1971) reported on 100 aphakic patients who had angiograms 4 to 16 weeks after cataract extraction. Forty per cent of the angiograms showed dye leakage in the macula with a maximum incidence six to eight weeks postoperatively. When repeat angiograms were available at the twentieth week postoperatively, two-thirds of the patients initially demonstrating leakage had reverted to normal. Two subsequent studies (Hitchings, Chisholm, and Bird, 1975; Hitchings and Chisholm, 1975) demonstrated an approximately 50 per cent incidence of fluorescein leakage from perifoveal capillaries six weeks postoperatively.

The present prospective study was undertaken to investigate further the incidence and time course of perifoveal capillary leakage after cataract surgery. Factors associated with the presence of leakage were also investigated.

Patients and methods

During the 15-month period from December 1973 to February 1975, fluorescein angiograms were performed on patients two weeks after cataract extraction and, if possible, again six weeks postoperatively. Intracapsular extractions were attempted in all cases. Approximately 50 per cent of the patients undergoing cataract extraction during this period had angiography. Reasons for patients not being included in the study were their inability to co-operate, refusal to participate, or inability to schedule angiography. The patients comprising this sample did not differ in age, race, or sex from the total operated population during that period, so that no bias of ascertainment existed. Furthermore, the percentage of patients in this sample who had operative complications was the same as a group of unselected patients undergoing cataract extraction (Maumenee and Meredith, 1974).

Before surgery all patients studied had a complete medical history; physical examinations included blood count and urine analysis. Each had a complete ocular history and examination which included visual acuity, refraction, external examination, slit-lamp examination, gonioscopy, central and peripheral visual fields, and dilated fundus examination. Thorough ocular examinations were carried out at the time of discharge and at each postoperative visit when angiography was performed.

Angiography was performed by the standard technique used at the Wilmer Ophthalmological Institute; 5 ml of 10 per cent sodium fluorescein is injected intravenously, photographs of the posterior pole are taken 5 seconds after injection and every second thereafter for 15 more seconds. Additional photographs are taken up to one minute at 3 to 5 second intervals, and repeated at 2, 5, 10, and 30 minutes. The Zeiss fundus camera with Allen stereo separator and Kodak Tri-X film were used. Stereo colour fundus photographs were taken in all cases. Angiograms were evaluated independently by two separate observers who had no knowledge of the patient's systemic condition or ocular history.

Patients were not included in the study if there was any ocular condition present known to be associated with macular oedema. Thus, three patients with mild diabetic retinopathy, one patient with an old branch vein occlusion, and one patient with retinitis pigmentosa were excluded although they all demonstrated leakage of fluorescein dye from perifoveal capillaries. Patients

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Address for reprints: Travis A. Meredith, MD, Department of Ophthalmology, Medical College of Wisconsin, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226, USA were also excluded if they had macular scarring from other lesions which interfered with the interpretation of the angiogram. Several angiograms were excluded because their quality was inadequate for precise interpretation.

Results

The 44 patients included in this study comprised 20 men and 24 women; 33 patients were Caucasian, and 11 were Black. The average age was 63 years (range 42 to 79 years).

Fluorescein angiograms done two weeks after cataract extraction were available on 50 eyes of the 44 patients. At this time, perifoveal capillary leakage was present in 30 out of 50 eyes (60 per cent) and in 25 of 44 patients (56 per cent). Six weeks postoperatively, follow-up angiograms were available on 17 eyes. Twelve of these eyes had initially demonstrated leakage at two weeks and 11 continued to leak at six weeks. None of the five patients negative at six weeks had shown leakage in angiograms two weeks after surgery.

The pattern of leakage varied widely throughout the series. Some patients showed only mild or moderate perifoveal capillary staining (Fig. 1) three to five minutes after injection, whereas others demonstrated extensive leakage with marked pooling in cystoid spaces in films taken 15 to 20 minutes postinjection. None of the patients with leakage demonstrated the dilatation of perifoveal vasculature noted in some cases of chronic cystoid oedema. Thus, perifoveal vascular dilatation may indicate a degree of chronicity that may be the hallmark of more severely damaged vessels.

VASCULAR DISEASE

Fourteen patients had either demonstrable cardiovascular disease or diabetes mellitus. Seven of these patients had adult-onset diabetes mellitus requiring medication but did not have background diabetic retinopathy. Three had hypertension requiring medication. Two had both diabetes and hypertension. Two had arteriosclerosis manifested by cardiac changes. Thirteen of the 14 patients with vascular disease (93 per cent) demonstrated perifoveal capillary leakage. Of the 30 patients without cardiovascular disease, only 12 (40 per cent) showed leakage. This difference is statistically significant at the $P < 0.001$ level.

AGE

Of 11 patients under the age of 60 years, only two (18 per cent) demonstrated dye leakage, and both had cardiovascular disease. Of the 33 patients who were 60 years of age or older, 23 (70 per cent) demonstrated leakage (Fig. 2*a*). When the data are corrected by excluding patients with the previously identified risk factor of vascular disease which is associated with leakage, none of the nine patients under 60 years showed abnormal capillary permeability, while 12 of the 21 patients (57 per cent) who were 60 years of age or older demonstrated leakage (Fig. 2*b*). This difference is statistically significant at the $P < 0.001$ level.

BILATERALITY

Six patients had bilateral cataract extractions. Five patients were positive for abnormal leakage in both

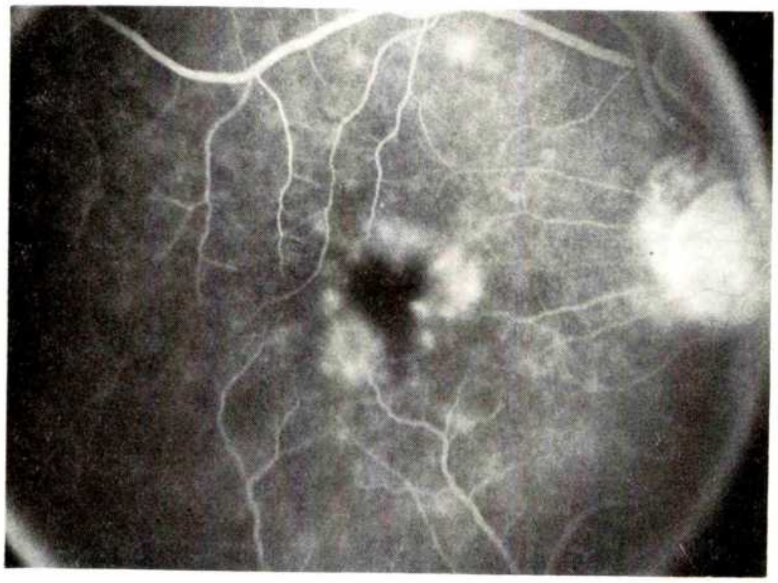


FIG. 1 *Fluorescein angiography at two weeks after uncomplicated intracapsular cataract extraction. Moderate perifoveal leakage is apparent seven minutes after fluorescein injection*

FIG. 2a *Age distribution of all patients with leakage (solid bar) and without leakage (hollow bar) at two weeks postoperatively*

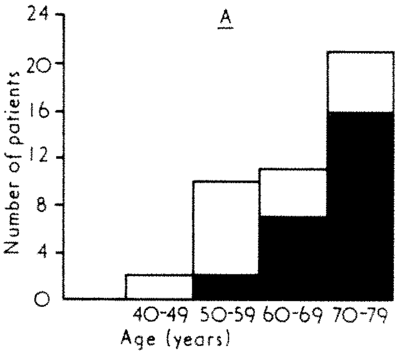
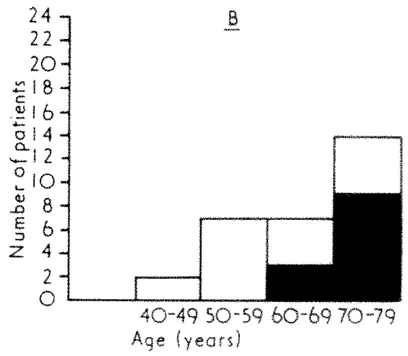


FIG. 2b *Age distribution of patients not having systemic vascular disease with leakage (solid bar) and without leakage (hollow bar) at two weeks postoperatively*



eyes, and three of these five had vascular disease. One patient did not show leakage in either eye.

ANTERIOR VITREOUS FACE

Specific comments about the condition of the anterior hyaloid face at the time of initial angiography were available for 34 eyes. Of 30 eyes with an intact vitreous face, 16 (53 per cent) showed leakage. Of four eyes with ruptured anterior hyaloid membrane, three of four (75 per cent) demonstrated leakage.

Late rupture of the anterior hyaloid face occurred in three patients with resultant vitreous to the wound. All three patients had previously developed vision equal to or better than 20/40, and all had demonstrated perifoveal capillary leakage before the time of the vitreous face rupture. Two of the three patients suffered a later decline in visual acuity associated with clinically apparent cystoid macular oedema. A fourth patient who had initially demonstrated no dye leakage developed a ruptured anterior face resulting in complete filling of the anterior chamber with vitreous. No change in vision resulted, and the follow-up angiogram remained negative.

OPERATIVE AND POSTOPERATIVE COMPLICATIONS

Two patients had inadvertent extracapsular extractions with vitreous loss. Both had anterior vitrectomies, and neither had vitreous to the wound. One had abnormal capillary leakage at the two-week angiogram, and one had not. Two patients had inadvertent extracapsular extractions without loss of vitreous, and neither had perifoveal leakage. Two patients developed postoperative hyphaemas, and both demonstrated leakage on angiography. One patient was discovered to have a cyclodialysis cleft postoperatively. The intraocular pressure was normal on the day of an angiogram which showed no leakage.

VISUAL ACUITY

At the time of initial angiography, there was no difference in the visual acuities between the group of patients demonstrating leakage and those who did not (Fig. 3*a*). At six weeks, all five eyes not obtaining acuity of 20/40 or better had shown leakage in the two-week angiogram (Fig. 3*b*).

ANTERIOR SEGMENT

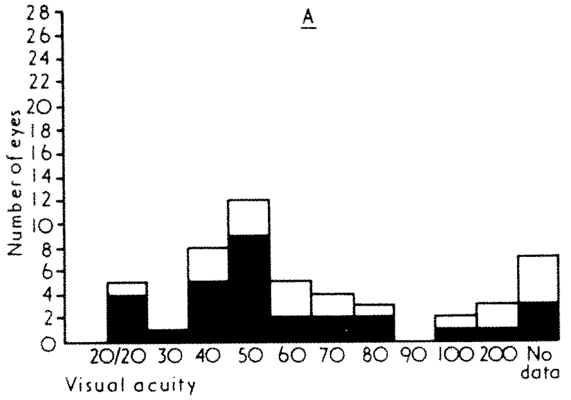
Subjective assessment of external injection and anterior chamber reaction (rated 0 to 4+) were made at the time of discharge from the hospital and at each postoperative visit. Most patients demonstrated 0 to 1+ inflammation at the time of initial angiography, and there was no difference in apparent inflammation between the group of patients who showed dye leakage and the group who did not. Of the 11 patients who demonstrated leakage at the six-week angiogram, only one was judged to have either external or anterior chamber inflammation.

INTRAOCULAR PRESSURE

Intraocular pressure was determined preoperatively, at hospital discharge, and at each postoperative visit. The difference in the preoperative and postoperative values was determined for each patient. The range of values and the mean values were the same for the group of patients who showed leakage as for the group who did not, both at discharge and at time of angiography. There were no cases of persistent hypotony in either group.

Discussion

This study confirms previous reports showing a high incidence of fluorescein leakage from perifoveal capillaries after cataract extraction (Irvine and others, 1971; Hitchings and others, 1975; Hitchings and Chisholm, 1975). These earlier reports have



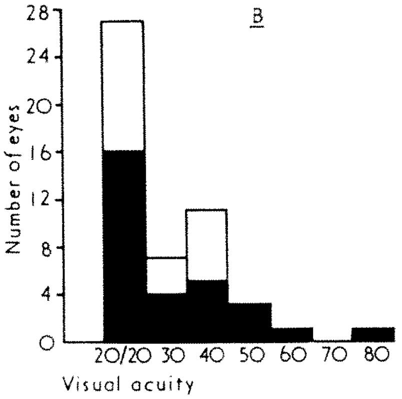


FIG. 3a *Distribution of visual acuities two weeks postoperatively in all eyes with leakage (solid bar) and without leakage (hollow bar)*

FIG. 3b *Distribution of visual acuities six weeks postoperatively in all eyes with leakage (solid bar) and without leakage (hollow bar)*

either indicated or assumed that leakage would reach maximal incidence at six weeks postoperatively, a time when patients are frequently found to have symptomatic reduction in visual acuity with ophthalmoscopically visible cystoid spaces in the macula. Our study indicates that leakage consistently develops within two weeks after operation and almost uniformly continues to be present six weeks postoperatively (11/12 eyes). In particular, we did not encounter leakage at six weeks that had not been present at two weeks, and there is no statistical difference in the percentage of patients found to be leaking at two weeks in our study and at six weeks in the studies by Hitchings and others (1975) and Hitchings and Chisholm (1975). We have subsequently observed fluorescein leakage to be present as early as five days after cataract extraction (unpublished observation).

A study (Klein and Yannuzzi, 1976) which noted only classic 'cystoid oedema of the macula' found a small percentage (5 per cent) of positive angiograms in the first week. Most of our cases demonstrated only mild degrees of perifoveal leakage in the early angiograms. Some of these progressed to demonstrate the more advanced changes of dilated cystic spaces in the macula on the six-week angiograms, while in others the amount of leakage remained the same or decreased.

Vascular disease in the form of hypertension, arteriosclerosis, and diabetes mellitus was shown to be a significant factor associated with altered capillary permeability in the early postoperative period. This implies that pre-existing disease of small vessels renders them more susceptible to develop leakage after cataract extraction, although leakage from these vessels before lens extraction cannot be ruled out.

The firm association of leakage with the factors of vascular disease and age, coupled with the negative correlations with operative and postoperative complications, inflammation, and intraocular pressure suggest that constitutional factors are important in precipitating abnormal vascular permeability during the early postoperative period. The identical angiographic behaviour of both eyes in each of the six patients studied bilaterally further supports this conclusion.

Perifoveal capillary leakage is compatible with 20/20 acuity. However, all five patients in this series who were not correctible to 20/40 six weeks postoperatively had had leakage demonstrable by the second postoperative week. If the criteria of reduction of vision and fluorescein dye leakage from perifoveal capillaries after cataract extraction are used to define the Irvine-Gass syndrome, then the present series demonstrates an approximately 10 per cent incidence.

While our data indicate that age and vascular disease are important factors in altered permeability of perifoveal capillaries in the early postoperative period, we are unable to identify precisely the cause of persistent dye leakage and decreased visual acuity. Gass and Norton (1969) identified operative complications, irido-vitreal abnormalities, inflammation, and vascular disease in a large proportion of their patients with aphakic macular oedema. Our patients with operative and postoperative complications did not consistently demonstrate early dye leakage, but the number of such patients in this series is too small to draw statistically significant conclusions.

The precise role of inflammation is also not clear. Our patients with dye leakage did not show any more anterior segment inflammation than did patients without leakage. Ten of 11 patients with leakage apparent in the six-week angiogram had no detectable inflammation at that time. Other reports have also indicated that clinical signs of anterior segment inflammation are often absent (Gass and Norton, 1969; Tolentino and Schepens, 1965). Vitreous inflammation, particularly the presence of cells in the posterior vitreous, has been considered important (Gass and Norton, 1969). In histopathologically studied cases, inflammatory changes of cyclitis, vitritis, and retinal phlebitis have been noted (Michels, Green, and Maumenee, 1971; Norton, Brown, Carlson, Pilger, and Riffenburgh, 1975; Martin, Green, and Martin, personal communication). These findings of widespread intraocular inflammation seemingly complement the clinical indications of the importance of vascular factors in the development of this syndrome.

Once leakage is established, it is possible that its persistence in a degree sufficient to cause decreased visual acuity is promoted by inflammation and/or irido-vitreal abnormalities. This possibility is illustrated in one of our patients, a 78-year-old diabetic man who had 20/40 vision despite perifoveal capillary leakage six weeks postoperatively. Five months postoperatively, however, delayed rupture of the anterior hyaloid face had occurred with vitreous to the wound, irritation, and subsequent reduction of acuity to 20/70. Angiography again demonstrated perifoveal capillary leakage.

Vascular factors may be important in sustaining leakage as well as causing it early in the postoperative period. Gass and Norton (1969) demonstrated vascular disease in 75 per cent of their patients with cystoid macular oedema and in 13 of 14 patients whose oedema did not resolve within the period of their study. It is possible that vascular factors also account for sufficient leakage to cause decreased acuity in quiet eyes with no inflammation or irido-vitreal abnormalities. Aphakic cystoid macular oedema may thus represent the final common pathway of several separate although sometimes related factors which result in altered perifoveal capillary permeability.

Summary

Perifoveal capillary leakage of fluorescein was demonstrated in 60 per cent of 50 eyes when angiography was performed two weeks after cataract extraction. Repeat angiography six weeks postoperatively in 17 eyes demonstrated persistence of already established leakage in 11 of 12 eyes and no new leakage in five eyes previously negative. Cystoid macular oedema with visual acuity of less than 20/40 six weeks postoperatively occurred in five eyes (10 per cent).

Eyes of patients with vascular disease and those patients of 60 years or older were found to have altered vascular permeability significantly more frequently. Inflammation was no more severe or prevalent in those patients who demonstrated leakage and no inflammation was clinically apparent in 10 of 11 eyes demonstrating dye leakage six weeks postoperatively. We conclude that the constitutional factors of age and vascular disease are of prime importance in causing altered vascular permeability in the early postoperative period after cataract extraction; factors causing sustained leakage with reduction of visual acuity were not demonstrated.

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Copper metabolism in retinitis pigmentosa

D. K. GAHLOT, P. K. KHOSLA, P. D. MAKASHIR, K. VASUKI, AND N. BASU
From Dr Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi

Copper is widely distributed in nature and forms a constituent of most foodstuffs. An average daily diet of an adult contains about 2 to 5 mg of copper, and a large part of this ingested copper is excreted in faeces, its excretion through urine being negligible. According to Cartwright (1950) an adult human body contains a total of 100 to 150 mg of copper, and a major proportion of it is in mammalian plasma and circulates as caeruloplasmin. Scheinberg (1966) believed that caeruloplasmin played a role in the maintenance of zero copper balance in the body.

There appears to be a close correlation between copper and cellular activity in all living beings. It is known that an important connexion between copper and pigment formation exists (Underwood, 1956). As primary retinitis pigmentosa is apparently caused by a retinal pigmentary disturbance, a study of copper metabolism in patients suffering from this disease was undertaken. No report of such a study is available in the literature. In this paper the results of copper concentration in serum, caeruloplasmin concentration in plasma, and copper excretion in urine are reported and their possible interrelationship in the context of this disease is considered.

Material and methods

Fifteen patients with primary retinitis pigmentosa between the ages of 10 and 42 years were investigated. All of them belonged to middle class society eating a predominantly vegetarian mixed Indian diet. The diagnosis of all these cases was based on the positive results of the following parameters:

HISTORY

Each of these patients had a history of progressively increasing night blindness which had started early in the first decade. The night blindness did not respond to any conventional treatment and it was gradually followed by visual disturbances during the day. Some of the patients also had a positive family history.

FUNDUS PICTURE

A typical atrophic pale disc, attenuation of blood vessels, and pigment dispersal could be seen in all patients except two in whom there was only generalized mottling of the fundus (Table I).

VISUAL ACUITY AND VISUAL FIELDS

Six patients had visual acuities ranging from 6/9 to 6/24 with or without correction while in nine the visual acuity was 6/60 or less. Perimetry showed moderate to marked generalized constriction of fields in most of them, but one patient showed a ring scotoma and in another fields were within normal limits. In others perimetry was not possible because of poor vision (Table I).

ELECTRO-OCULOGRAPHY

Electro-oculography was performed according to the method of Gahlot and Hansen (1974), and each patient was found to have a very low ratio. In five electro-oculograms were not possible as the patients could not see the fixation light during the dark phase (Table I).

ELECTRORETINOGRAPHY

Electroretinographic responses, both scotopic and photopic, were recorded and it was found that in five cases these were subnormal, while in the remaining 10 they were flat (Table I).

OTHER TESTS

None of these patients had a positive history of any systemic infection and their reactions to tests for syphilis and tuberculosis were negative. Their erythrocyte sedimentation rates were normal and the urine did not show albumin, sugar, or acetone. These patients were subjected to the following biochemical tests:

All fifteen cases of primary retinitis pigmentosa (11 males and 4 females) were selected to determine their level of total serum copper. This was done using the method of Eden and Green (1940) and Ventura and King (1951) as modified by Varley (1975). Ten normal subjects were included as controls.

The caeruloplasmin concentration levels in plasma using the method of O'Brien and Ibbott (1964), a modification of Ravin (1961), were established by determining the copper oxidase activity in 10 patients (7 males and 3 females) and in 10 normal people as controls (Tables II and III). All glass instruments were thoroughly demineralized and all of them except the blood collection tubes were siliconized. The clear plasma was stored at 4°C before analysis but never for more than one week. The haemolysed sample was discarded.

Address for reprints: Dr D. K. Gahlot, Dr Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi-110016, India

Table I *Clinical and electrophysiological parameters for the diagnosis of retinitis pigmentosa*

Patient no.	*Age (years)*	*Sex*	*Visual acuity*		*Electroretinography*	*Electro-oculography ratio*		*Visual fields*	*Fundus*
			Right eye	*Left eye*		*Right eye*	*Left eye*		
1	21	Male	PL PR	PL PR	Subnormal	Not possible		Not possible	Pale, blood vessels attenuated, pigment + +
2	22	Female	6/9	6/9	Flat	115	110	Tubular	Pale, blood vessels attenuated, pigment + +
3	25	Male	6/36 =6/24	6/24 6/12	Flat	125	125	Tubular	Pale, blood vessels attenuated, pigment + +
4	25	Male	6/60 =6/9	6/36 6/9	Subnormal	100	115	Generalized constriction	Pale, blood vessels attenuated, pigment + +
5	25	Female	2/60	2/60	Flat	100	100	Tubular	Pale, blood vessels attenuated, pigment + +
6	28	Male	6/9	6/9	Subnormal	112	135	Generalized constriction	Pale, blood vessels attenuated, pigment + +
7	15	Male	PL PR	PL PR	Flat	Not possible		Not possible	Pale, blood vessels attenuated, pigment + +
8	21	Male	6/18	6/18	Flat	110	100	Generalized constriction	Pale, blood vessels attenuated, pigment + +
9	34	Female	6/60 =6/24	6/60 6/24	Subnormal	110	120	Ring scotoma	Pale, blood vessels attenuated, pigment + +
10	42	Female	6/60	6/60	Flat	100	100	Generalized constriction	Pale, blood vessels attenuated, pigment + +
11	22	Male	CF 1m	6/60	Flat	115	120	Generalized constriction	Pale, blood vessels attenuated, pigment + +
12	25	Male	CF ½m	CF ½m	Flat	Not possible		Not possible	Pale, blood vessels attenuated, generalized mottling No pigmentation
13	42	Male	CF 1m	CF 1m	Flat	110	110	Not possible	Pale, blood vessels attenuated, pigment + +
14	10	Male	PL PR	PL PR	Flat	Not possible		Not possible	Pale, blood vessels attenuated, generalized mottling
15	22	Male	CF 2m	CF 2m	Subnormal	Not possible		Normal	Pale, blood vessels attenuated pigment + +

Flat — Extinguished; = — Improves to; PL — Perception of light; PR — Projection of rays; CF — Counting fingers

Copper excretion in urine was determined using the method of Gubler, Lahey, Aschenbruker, Cartwright, and Wintrobe (1952) as modified by Henry (1968). Ten patients (8 males and 2 females) and five normal subjects were included (Tables IV and V).

Observations

SERUM COPPER CONCENTRATION

The results showed that the concentration of total copper in the serum of normal subjects varied from 60 to 150 µg/100 ml of serum, 97·7 ± 27·13 (n = 10). However, the copper concentration in patients with retinitis pigmentosa varied from 36 to 108 µg/100 ml of serum, 77·6 ± 22·89 (n = 15). This showed that the mean figure in these patients was not significant at 5 per cent level (P ≃ 0·08) although individually some of them had figures lower than normal.

PLASMA CAERULOPLASMIN CONCENTRATION (Tables II and III)

The caeruloplasmin in optical density units in normal subjects ranged from 0·19 to 0·31 (mean 0·23) while that in patients ranged from 0·15 to 0·03 (mean 0·08). Converting the average figures of optical density units in terms of caeruloplasmin concentration in mg (Ravin, 1961) gives 20·12 mg/100 ml for normal subjects and 7·0 mg/100 ml for patients. This showed that the concentration of caeruloplasmin in the plasma of patients with retinitis pigmentosa was significantly lower (P < 0·001).

COPPER EXCRETION IN URINE (Tables IV and V)

The results show a striking and statistically significant increase in urinary excretion of copper in patients with retinitis pigmentosa compared with normal subjects (P < 0·001).

Table II *Plasma caeruloplasmin concentration in optical density units in normal subjects*

Subject no.	*Age (years)*	*Sex*	*Caeruloplasmin*
1	26	Female	0·19
2	32	Female	0·31
3	22	Female	0·22
4	35	Female	0·19
5	32	Male	0·20
6	26	Male	0·28
7	40	Male	0·21
8	30	Male	0·21
9	25	Male	0·20
10	27	Male	0·31

Mean = 0·23; SD = 0·049

Table III *Plasma caeruloplasmin concentration in optical density units in patients with retinitis pigmentosa*

Patient no.	*Age (years)*	*Sex*	*Caeruloplasmin*
1	25	Male	0·15
2	25	Female	0·09
3	10	Male	0·06
4	15	Male	0·07
5	21	Male	0·06
6	25	Male	0·08
7	34	Female	0·07
8	42	Male	0·03
9	42	Female	0·13
10	10	Male	0·07

Mean = 0·08; SD = 0·035; P<0·001 highly significant

Discussion

The plasma concentration of copper in Americans and Europeans is about 100 µg/100 ml of plasma (range 75 to 160 µg/100 ml) (Gubler, 1956; Markowitz, Gubler, Mahoney, Cartwright, and Wintrobe, 1955; Underwood, 1956; Varley, 1975). This corresponds well with the current figures for normal Indian subjects. Blood contains two principal fractions of copper. About 6 per cent is loosely bound to serum albumin while 94 per cent is tightly bound to serum globulin as caeruloplasmin fractions. When copper first enters the plasma from the gastrointestinal tract it is believed to be loosely bound to albumin and is gradually transferred in the liver to caeruloplasmin. Some is present as free cupric ion which is in equilibrium with copper loosely bound to albumin. The loosely bound copper is probably the portion being transferred because unlike copper bound to caeruloplasmin it can diffuse freely across semipermeable membrane and appears in urine. From plasma, copper goes to several sites in the body and exists in many forms *in vivo*, the total function of which is not yet known.

Copper metabolism seems peculiarly susceptible to alterations in a wide variety of clinical conditions. Many conditions are accompanied by a marked increase in plasma copper such as most chronic infections, myocardial infarction, hyperthyroidism, hepatitis, post-hepatitis cirrhosis, portal cirrhosis, iron deficiency anaemia, hypoproteinaemia, pellagra, chronic alcoholism, schizophrenia, Hodgkin's disease, scleroderma, leukaemias, and carcinoma (Scheinberg and Sternlieb, 1960). Like erythrocyte sedimentation rate and white blood corpuscle count, serum copper is an acute phase reactant and is probably related to the general metabolic state of the tissue. The condition of hypercupraemia is usually associated with a corresponding rise in caeruloplasmin concentration because a major part of copper exists in the body as a component of caeruloplasmin. However, the exact relationship is not clear. The occurrence of low serum copper levels is less frequent than high levels. Hypocupraemia in humans occurs in new-born infants, sprue, nephrotic syndrome, and hepatolenticular degeneration (Scheinberg and Sternlieb, 1960). It appears that hypocupraemia is caused by a decrease in the concentration of caeruloplasmin.

Table IV *Copper excreted in the urine of normal subjects in 24 hours*

Subject no.	*Age (years)*	*Sex*	*Urine (µg/24h)*
1	30	Male	11
2	40	Male	38
3	29	Male	46
4	23	Male	40
5	24	Male	25

Mean = 32 µg/24h; SD = 14·02

Table V *Copper excreted in the urine of patients with retinitis pigmentosa in 24 hours*

Patient no.	*Age (years)*	*Sex*	*Urine (µg/24h)*
1	45	Male	156
2	25	Male	170
3	35	Female	169
4	10	Male	213
5	15	Male	260
6	25	Male	222
7	8	Male	200
8	12	Female	180
9	42	Male	151
10	22	Male	240

Mean = 186·1 µg/24h; SD = 54·28; P<0·001 highly significant

Caeruloplasmin is an alpha-globulin and accounts for most of the copper ions and oxidase activity of blood which in turn varies with the serum copper levels. The exact nature of physiological function of caeruloplasmin is not known except that, being a member of the copper enzyme system in the body, it is in some way related to the oxidative processes of the tissue, probably at the mitochondrial level.

No report is available in the literature in which the copper metabolic state in patients with primary retinitis pigmentosa has been studied and, therefore, no figures are available on their serum copper and caeruloplasmin concentrations or their copper urinary excretion. The observations in our study show that all the patients had either normal or low serum copper concentration although the average figure was not significantly lower than normal. This normal or near normal figure was associated with a highly statistically significant low copper oxidase activity—that is low caeruloplasmin concentration. Furthermore, in our series all the patients showed a very greatly increased excretion of copper in the urine.

The amount of copper excreted in normal human urine varies considerably but the different techniques used with the possibility of contamination with extraneous copper may contribute to the divergent results. Rabinowitch (1933) reported from 'traces' to 700 µg/24h while Munch-Peterson (1950) and Keltz (1959) found 120 to 520 µg/24h for adults and 20 to 90 µg/24h for children. Van Revesteyn (1944) reported 0 to 100 µg/24h while Heilmeyer, Keilerling, and Stuwe (1941) could find only 'the most minimal traces' of copper in urine. The preponderance of recent evidence, however, indicates that urinary copper excreted is about 0 to 30 µg/24h (Porter, 1951; Mahoney, Bush, Gubler, Moretz, and Cartwright, 1955; Butler and Newman, 1956). The output is considerably higher if there is concomitant proteinuria (Uzman and Denny Brown, 1948). Chatterjee and Ganguly (1950) observed that an Indian excreted less copper in urine than a European probably because of differences in diet.

An absolute magnitude of urinary copper excretion is of special interest since increased urinary excretion of copper is seen only in hepatolenticular degeneration (Mondelbrote, Stainer, Thompson, and Thruston, 1968; Porter, 1949; Cumings, 1951) and nephrotic syndrome with albuminuria (Cartwright and Gubler, 1954).

Munch-Peterson (1950) analysing urinary excretion in nephritis and other conditions causing proteinuria found a rough linear correlation between amounts of copper and protein excreted. It appears that an increase in urinary copper in association with proteinuria could be accounted for by an abnormal leak through the glomeruli of the copper protein found in the plasma. This cannot account for the small amount of excreted copper found in normal subjects nor for the greatly increased excretion in hepatolenticular degeneration. In retinitis pigmentosa this is still more difficult to explain because our preliminary investigations showed that there was no gross deficit in the kidney functions in patients nor was there any significant proteinuria.

Thus our series of patients of primary retinitis pigmentosa show a triad of interesting findings:

Normal or near normal serum copper concentration,
Significantly low caeruloplasmin concentration,
High urinary copper excretion.

These findings are important because they have so far not been reported and this combination of findings is a feature of chronic copper toxicity as seen in hepatolenticular degeneration. Liver biopsy studies conducted in some cases of retinitis pigmentosa have also shown a few mild non-specific changes indicating that in primary retinitis pigmentosa copper metabolism may also be abnormal.

An attempt was made at producing a condition similar to retinitis pigmentosa in monkeys and rabbits by injecting them with a copper sulphate solution, and details will be published later. The condition histologically appears to simulate some feature reported for sodium iodate and iodacetate indicating that copper may be acting in the same manner as these toxic substances. Copper is a strong inhibitor of the sulphhydryl group which is an essential cofactor in the metabolic pathways of glycolysis and necessary for the regeneration of visual purple.

The clinical importance of such an hypothesis is obvious. If it is true, the use of a chelating agent—such as penicillamine—may gradually improve the condition. On this assumption one of us (DKG) actually began treatment on two patients in this series although the follow-up of a few months is too short to judge the response. It thus appears that retinitis pigmentosa may not be an abiotrophy but a condition of chronic copper toxicity due to an inborn error of copper metabolism.

Summary

Clinically and electrophysiologically confirmed cases of primary retinitis pigmentosa have been investigated regarding their copper metabolic state. It is observed that these patients show a normal or near normal serum copper concentration, very low plasma caeruloplasmin concentration, and a very high copper urinary excretion. A similarity between

this condition and hepatolenticular degeneration is drawn and it is suggested that retinitis pigmentosa may also be a condition caused by an inborn error of copper metabolism.

We are grateful to Professor Lalit P. Agarwal, Chief Organizer of Dr Rajendra Prasad Centre for Ophthalmic Sciences, for providing the facilities. We are also indebted to Dr N. N. Sood for his valuable comments. Our thanks are also due to Professor O. P. Ghai, Dr S. K. Sood, and Dr N. K. Bhide, All-India Institute of Medical Sciences, for giving us the facilities of their laboratories and to Mr H. S. Varma and Shyam Sunder for providing the technical assistance.

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Retinitis pigmentosa and Coats's disease

I. AYESH*, M. D. SANDERS, AND A. I. FRIEDMANN
From the Medical Ophthalmology Unit, St Thomas's Hospital, London

The association of two rare ocular conditions of unknown aetiology presents the clinician with an opportunity to study interrelating factors. The association of retinitis pigmentosa with Coats's disease has been previously reported in three patients (Zamorani, 1956; Morgan and Crawford, 1968), in all of whom bilateral involvement occurred with severe visual loss.

The present case which has been fully documented demonstrates the association of bilateral retinitis pigmentosa with retinal telangiectasia (Coats's disease) and drusen of the optic disc.

Case report

A 15-year-old girl was seen at the Medical Ophthalmology Unit in July 1973 with a 10-year history of impaired vision and recent further deterioration.

HISTORY

The patient's birth had been normal although two weeks premature and her early development had also been normal. At the age of five years she was found to be deaf in her right ear and her parents also noticed she had poor vision in dim light. In July 1970 at the age of 12 years she was admitted to the Medical Ophthalmology Unit. Visual acuity was 5/60 and N8 in the right eye and 6/18 and N8 in the left; colour vision was reduced in both eyes. Peripheral visual fields were markedly constricted.

Fundus examination showed exposed drusen of the right disc and buried drusen of the left, and a widespread pigment epithelial disturbance with a few clumps of intraretinal pigment deposition. The choroidal vessels were visible and a serous detachment was present inferiorly in the right eye.

There was no family history of retinitis pigmentosa or consanguinity although electrodiagnostic tests performed on her two younger sisters showed a slightly subnormal light rise in the electro-oculogram (light rise right eye 228 per cent, left eye 210 per cent in the 12-year-old sister; right eye 243 per cent, left eye 200 per cent in the 10-year-old sister).

OCULAR FINDINGS

In July 1973 the visual acuity in the right eye was 5/60 and N8 and in the left 6/60 and N8 with correction. The peripheral visual fields showed marked constriction to 5° from fixation on each side, and the central fields showed severe loss of visual function including severely diminished macular thresholds (Friedmann analyser). Fundus examination showed exposed drusen of the right optic disc and widespread degeneration of the retina and pigment epithelium including the macular region. There were bilateral inferior serous detachments with dilated and tortuous retinal vessels. Fluorescein angiography (Fig. 1) demonstrated good filling of the retinal arterioles which were of normal calibre, and the inferior vessels appeared relatively larger than the superior vessels. Choroidal fluorescence was visible through the deficient pigment epithelium. The retinal vessels in the inferior fundus on both sides were dilated and tortuous particularly in the periphery, with capillary dilatation and microaneurysm formation. Extensive retinal and subretinal leakage of dye was visible (Fig. 2).

Electrodiagnostic studies

Both the scotopic and photopic electroretinograms were almost totally extinguished with the highest intensity evoking only a very small response. The electro-oculogram was flat in both eyes. Laboratory data including plasma electrolytes, plasma proteins, Wassermann reaction and Kahn's test were all normal.

Discussion

The association of retinitis pigmentosa and Coats's disease was first described by Zamorani (1956) in a 16-year-old girl. Zamorani's patient had a fully developed cataract in the eye so that fundus changes were visible on only one side, and drusen of the disc was not observed. Electrodiagnostic tests were not performed.

Two further cases were described by Morgan and Crawford (1968) with typical pigment epithelial degeneration and retinal arteriolar narrowing. The inferior vessels were dilated and irregular and there were inferior serous detachments. Electroretinograms were extinguished and fluorescein angiography was not performed.

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*Department of Ophthalmology, King Hussein's Medical Centre, Amman, Jordan

Address for reprints: M. D. Sanders, Medical Ophthalmology Unit, St Thomas's Hospital, Lambeth Palace Road, London SE1 7EH

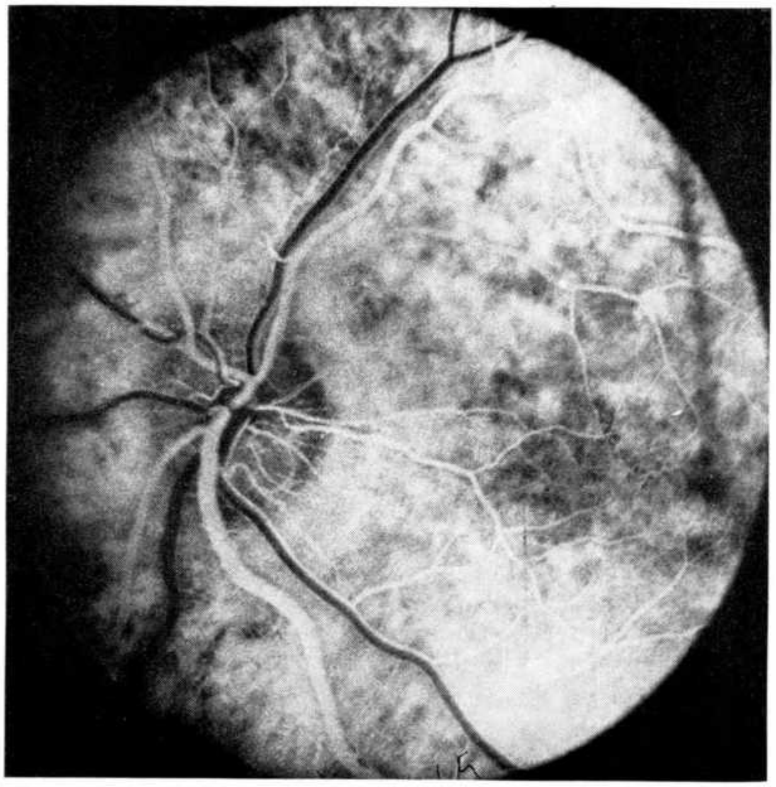

FIG. 1 *Arterial and early venous phase of the fluorescein angiogram, inferior retinal vessels appear larger than superior vessels. Note widespread pigment epithelial disturbance and the patchy choroidal fluorescence*

The case now reported shows the association of pigmentary degeneration with inferior retinal telangectasia and massive exudation (Coats's disease). Fluorescein angiography shows the dilated and tortuous arteries and veins with numerous microaneurysms. Electro-oculography in this family showed mild impairment of light rise in two sisters, although a brother similarly tested at the same time had normal results. These findings raise the possibility that the two sisters are carriers suggesting a recessive mode of inheritance.

Retinitis pigmentosa is a bilateral hereditary disorder of the retinal receptors and pigment epithelium which may be present from birth. Numerous associations with systemic conditions are reported (Alstrom, 1959), and in some a specific metabolic disorder is described, as in Refsum's syndrome (Refsum, 1946). Drusen of the disc may be associated in a few (0·3 to 2 per cent) cases (Lorentzen, 1966). Pathological evidence in the tapeto-retinal disorders suggests a primary degeneration of the receptors and pigment epithelium. Several aetiological mechanisms have also been implicated for drusen of the disc including degeneration of axons (Seitz and Kersting, 1962), degeneration of neuroglia (Fuchs, 1926), and migration of the pigment epithelium (Lauber, 1921).

In contrast Coats's disease is a rare unilateral disease without any hereditary pattern or systemic associations which develops in the second and third decades. Recent electron microscopical findings, however, suggest a primary defect in the vascular endothelium producing increased permeability (Tripathi and Ashton, 1971) and resultant massive exudation. Dilatation of the retinal feeder vessels in our patient might be explained by the increased perfusion. The presence of bilateral retinal telangectasia with tapeto-retinal degeneration and drusen in a number of reports suggests a possible linked association. Although speculative, this could be explained as a primary degeneration involving the retinal vessels, the retinal axons, the retinal receptors, and pigment epithelium.

Summary

The association of bilateral retinitis pigmentosa, Coats's disease, and drusen of the optic disc has been described. Previous reports are discussed and the association could be explained as a degenerative condition involving retinal vessels, retinal receptors, and axons.

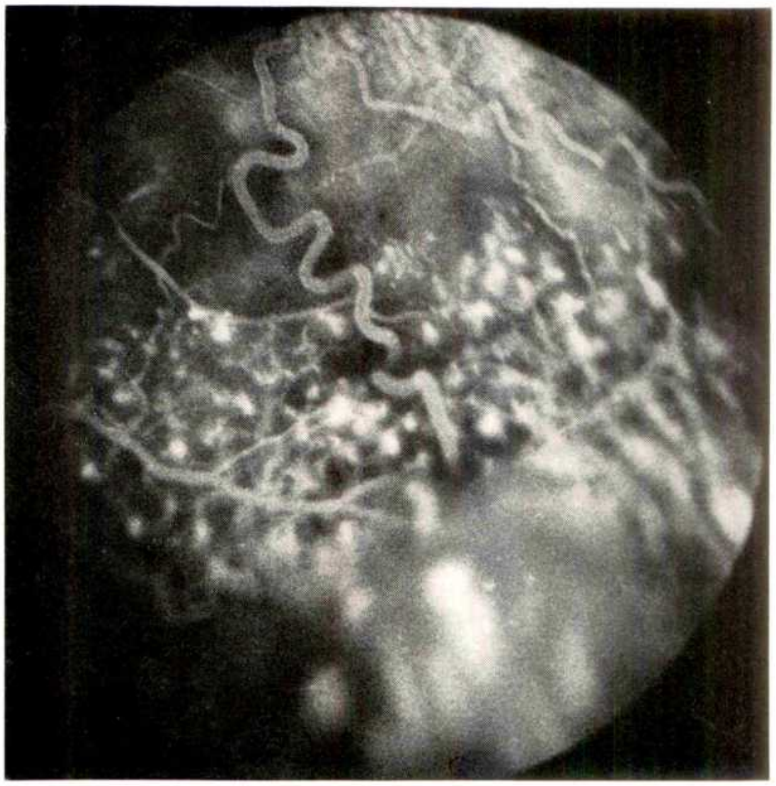

FIG. 2 *Venous phase and the dilated tortuous inferior temporal retinal vein is clearly seen with a shunt vessel*

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The optic disc in glaucoma
1: Classification

R. A. HITCHINGS
Moorfields Eye Hospital, City Road, London
AND
G. L. SPAETH
Wills Eye Hospital, Spring Garden Street, Philadelphia 19130, *USA*

The pale, cupped disc found in the final stages of glaucomatous disease has been known from the time of Von Graefe (1854). Since then many observers have described changes that occur at the optic disc in chronic, simple glaucoma. There has been particular interest in changes which may occur in the early stages of the disease.

Studies of the normal population have shown that while there is a wide diversity in the appearance of the normal optic disc, in a single subject (Armaly, 1969; Fishman, 1970; Kolker and Hetherington, 1970; Portnoy, 1973) the two discs are remarkably similar (Witsiuk, 1966; Kronfeld, 1970; Woodruff, 1970; Portnoy, 1973). In contrast, individuals with glaucomatous disease usually show manifest asymmetry of the two optic discs (Fishman, 1970; Kolker and Hetherington, 1970).

Many criteria have been used to describe the glaucomatous optic disc. Important among these is the ratio of the cup diameter to the diameter of the entire disc (Pickard, 1923; Snydacker, 1964; Hollows and McGuiness, 1967; Armaly, 1967, 1968; Schwartz, 1973; Tomlinson and Phillips, 1974). This was initially measured horizontally, but recently measurement of the vertical cup to disc (C/D) ratio has been stressed, after recognition that changes in the optic cup tend initially to affect the vertical diameter (Chandler and Grant, 1965; Kronfeld, 1967; Kirsch and Anderson, 1973; Weisman, Assif, Phelps, Podos, and Becker, 1973).

Stereoscopic examination of the optic disc in early glaucoma reveals signs which help to distinguish the normal from the glaucomatous cup (Anderson, 1975; Reed and Spaeth, 1974). These signs are evidence for acquired tissue loss and account for the asymmetry previously noted. Tissue loss may appear in a variety of forms: thinning of the neuroretinal rim, either localized or generalized; depression or steepening of the walls of the cup (the tinted hollow (Reed and Spaeth, 1974) or saucer); deepening of the cup exposing the lamina cribrosa (the 'laminar dots' sign (Reed and Spaeth, 1974)); and change in the course of the retinal vessel which is seen as a sharp change in direction ('kinking' or bayoneting (Reed and Spaeth, 1974)). In addition, the presence of localized regions of nerve fibre loss or 'gutters' has been demonstrated in some cases of early glaucoma by Hoyt, Frisen, and Neuman (1973).

The aim of this paper was to assess systematically glaucomatous discs and look for those features that are commonly associated. As a result, five different types of optic disc appearance are described.

In this paper the term glaucoma has been used for all cases in which the intraocular pressure exceeded 22 mmHg and glaucomatous cupping was visible on stereoscopic examination of the disc. This has meant including cases in which the optic disc appeared normal by uniocular ophthalmoscopy, and even cases in which glaucomatous cupping was visible without detectable field loss.

Material and methods

This study was based on analysis of stereoscopic disc photographs of 252 patients from the files of the Glaucoma Clinic at Wills Eye Hospital. The patients were mostly cases of known or suspect glaucoma attending the Glaucoma Service. In addition, 25 normal patients on the files of the Glaucoma Service were included. The diagnosis was unknown at the time of analysis of the stereophotographs.

Most photographs were taken within an 18-month period using a Zeiss fundus flash II camera with a ×2·0 adaptor. Stereoscopic photographs were obtained after maximal pupillary dilatation by photographing the clear optic disc images obtained at each end of a horizontal traverse of the camera body. This traverse was usually 3 to 4 mm.

Slides were examined with a stereoscopic viewer. The stereo pairs of the two eyes were directly compared. Special note was made of identifying characteristics suggestive of tissue loss.

The following criteria were analysed:

Address for reprints: R. A. Hitchings, FRCS, Moorfields Eye Hospital, City Road, London EC1V 2PD

THE VERTICAL CUP/DISC (C/D) RATIO

The 'cup' was defined in terms of configuration; its extent was determined by drawing a hypothetical line vertically on the anterior surface of the disc from the most superior to the most inferior aspect of the disc margin; the segment of the line not in contact with the disc surface was considered to be 'the cup'. The ratio (expressed in tenths) of that segment to the length of the entire line was the 'cup/disc ratio' (C/D). Pallor of the optic disc played no part in the assessment of the C/D ratio (Schwartz, 1973).

THE WALLS OF THE OPTIC CUP

The specific points checked were: degree of inclination in the walls, variation in the slope of the walls of any one cup, and difference between cups of the two eyes in each patient. The presence of a more steeply-sided cup despite identical C/D ratios was considered suspicious of enlargement of the cup.

THE DEPTH OF THE OPTIC CUP

The depth of the optic cup was described as 'normal', 'deep', or 'bean-pot'. 'Normal' depth referred to an optic cup which did not show evidence of actual posterior bowing of the lamina cribrosa itself; the cup, however, could extend as far posteriorly as the 'laminar dots' (taken to represent the lamina cribrosa) described by Reed and Spaeth (1974). In a 'deep' cup the lamina cribrosa appeared posteriorly bowed. A 'bean-pot' cup, so called because of its likeness to a spherical clay pot, was diagnosed when posterior displacement of the lamina cribrosa coexisted with undermining of the neuroretinal rim; in transverse section the walls and base of the cup formed the major part of a circle. There was usually little difficulty distinguishing between a flat or a posteriorly-bowed lamina cribrosa. Similarly, although there was clearly a spectrum of changes, differentiation between the 'deep' and the 'bean-pot' cup was usually fairly straightforward. In those few cases where differentiation between two descriptive types was not easy, the shallower type of cup depth was chosen.

THE NEURORETINAL RIM

The pallor and the width of the neuroretinal rims were graded. The colour achieved with transparencies was not an exact match with the colours seen on stereoscopic examination, and pallor of the rim could not always be differentiated from the normal pinkish colour. As a result, comments on colour were restricted to recording whether the neuroretinal rim was pale or pink. Thinning of the neuroretinal rim was far more easily quantitated, and ranged from being just noticeable to a complete absence of rim tissue with extension of the cup to the outer disc margin. The size of the arc involved in thinning ranged from a localized segment (producing a 'notch') to circumferential thinning of the entire neuroretinal rim.

DISPLACEMENT OF THE RETINAL VESSELS

Distinction was made between a gradual curve of a retinal vessel as it passed over the surface of the optic disc and a sharp 'kinking' or change in the vessel's direction either in the same plane as the disc surface or at an angle to it. The gradual curve was considered normal; the kink was thought to be an acquired change that occurred secondary to enlargement of the optic cup. Kinking resulted in nasal displacement of the vessels, and was of most significance when it occurred at the outer margin of the disc.

PIGMENT CLUMPING

The presence or absence of pigment clumping around the margin of the optic disc was noted.

NERVE FIBRE LAYER

The nature of the nerve fibre layer was observed as far as possible within the limits of the examination technique. Where refractile lines taking the known pattern of the nerve fibre layer (NFL) were visible the NFL was thought to be present. If none of the gutters or grooves described by Hoyt and others (1973) was visible the NFL was called 'intact'. If such a gutter was observed it was listed as a nerve fibre bundle defect (NFBD). If no NFL could be seen at all it was called 'invisible'.

Results

Stereoscopic photographs from 504 eyes of 252 patients were analysed. The optic discs were divided into two groups, normal and pathological, this second being subdivided into five types of glaucomatous cupping (overpass, cupping without pallor of the neuroretinal rim, cupping with pallor of the neuroretinal rim, focal notching of the neuroretinal rim, and bean-pot cupping), whose characteristics will be described. The overall numbers and characterizing features are seen in the Table. Stereophotographs illustrating each of these examples may be seen in Figs 1–5.

CHARACTERISTICS OF DISC SUBTYPES

Normal disc

A disc was considered 'normal' in appearance if the neuroretinal rim was pinkish and of equal thickness throughout, or with its thinnest portion at the temporal margin on the horizontal meridian of the disc. There were no sharp deviations of any retinal vessel where it traversed the disc surface. This type of disc usually had a C/D ratio of less than 0·5, an optic cup of 'normal' depth (as defined above), and a visibly intact nerve fibre layer. When the two optic discs from any patient were highly symmetrical, they were considered 'normal'; this latter definition allowed optic discs with a C/D ratio greater than 0·5, a sharply deviating retinal vessel, or a poorly visualized nerve fibre layer to be included in this normal group. The optic discs of

Table *Clinical features of glaucomatous discs*

Type	*No.*	*Percentage of total*	*Vertical C/D*		*Cup depth*			*Incidence of overpass No.)*	*Notch (No.)*	*Rim pallor (No.)*	*Vessel displacement (Bayoneting) (No.)*	*Pigment clumping*		*Nerve fibre bundle defect (No.)*
			Range	*Mean*	*Normal*	*Deep*	*Bean-pot*					*(No.)*	*(Per cent)*	
1. Normal	231	46	0–0·6	0·3	223	6	—	27	0	0	6	27	(11)	222 Intact 9 Invisible
2. Overpass vessels	44	9	0·2–0·9	0·6	42	2		44	3	3	13	21	(65)	24 Intact 17 Invisible 3 NFBD
3. Cupping without pallor of rim	124	25	0·3–0·9	0·7	44	76	4	12	0	0	122	74	(61)	82 Intact 30 Invisible 12 NFBD
4 Cupping with pallor of rim	68	12	0·7–0·9	0·85	11	57	—	10	20	68	68	58	(82)	60 Invisible 8 NFBD
5. Focal notching	23	5	0·4–0·3	0·7	23	—	—		25	21	21	21	(91)	1 Intact 3 Invisible 19 NFBD
6. Bean-pot	14	3	0·9	0·9	—	—	14	0	0	13	14	13	(92)	13 Invisible 1 Intact

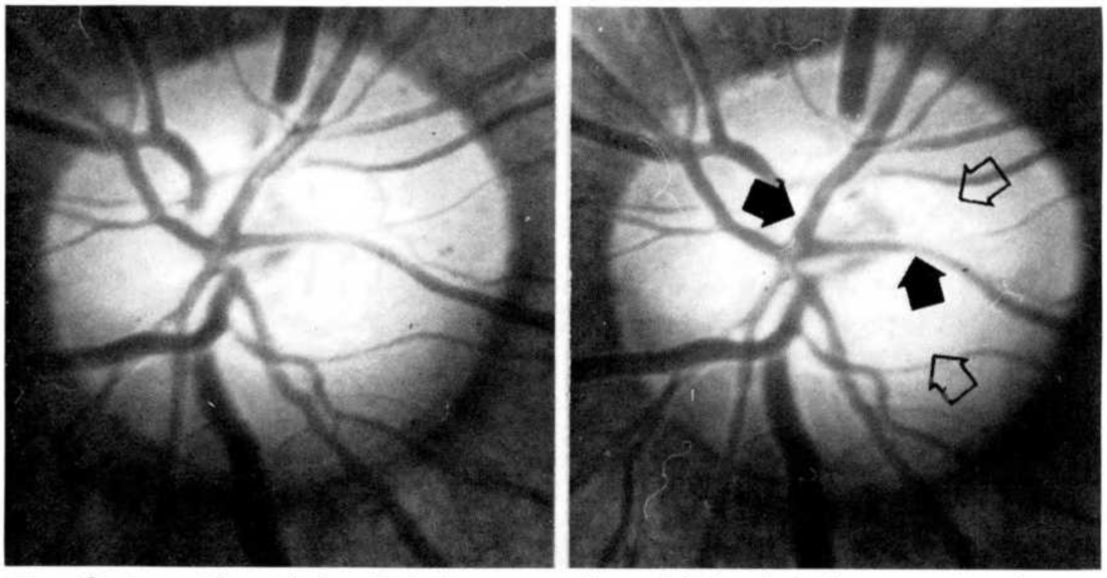

FIG. 1 *Overpass cupping; retinal vessels (dark arrows) pursuing a relatively undeviated course over the optic cup (hollow arrows)*

For satisfactory viewing these stereo pairs should be examined using a suitable convex sphere. With higher powers of sphere, fusion may be obtained by decentring the spheres. To do this, increase the distance between them

all 25 patients clinically considered normal fell into this category.

Overpass cupping (Kronfeld, 1967; Spaeth and Hitchings, 1975)

Where tissue loss within the optic nerve papilla was visible on stereoscopic examination, but *without* gross enlargement of the optic cup, the phrase 'overpass cupping' was used. This type of intrapapillary tissue loss occurred to a minor degree in some discs classed as 'normal'. More frequently, it involved the disc extensively, and the two discs asymmetrically, being the major anatomic abnormality visible on stereoscopic examination. In these cases the retinal vessels could be seen pursuing a

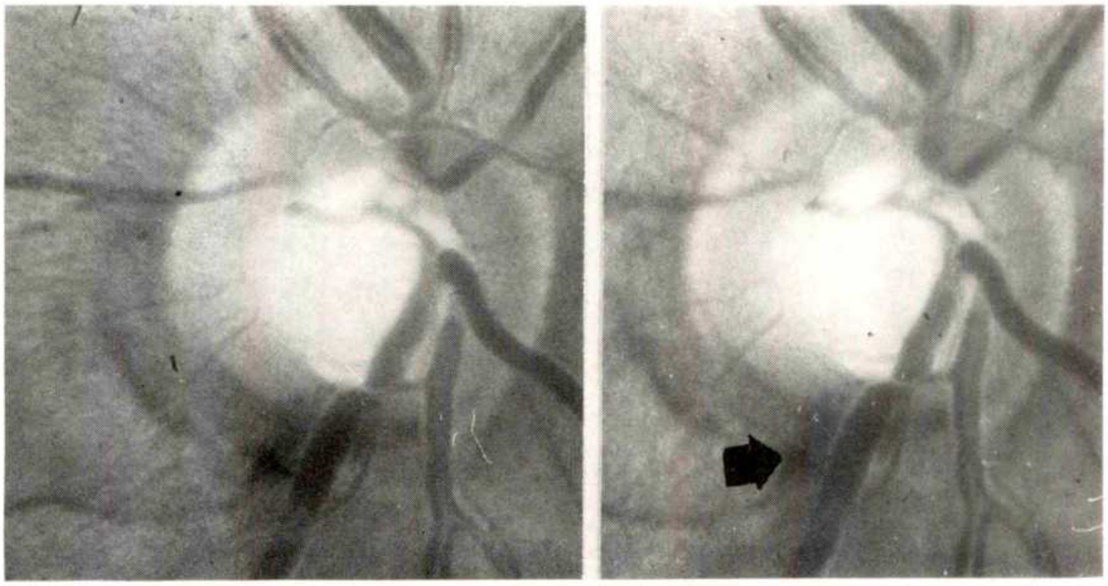

FIG. 2 *Cupping without pallor of the neuroretinal rim; glaucomatous cupping is suggested by localized (inferior) thinning of neuroretinal rim, steeply-sided walls to cup, an angulated course followed by infero-temporal vein around rim of cup, and, in this case, a splinter haemorrhage (arrow)*

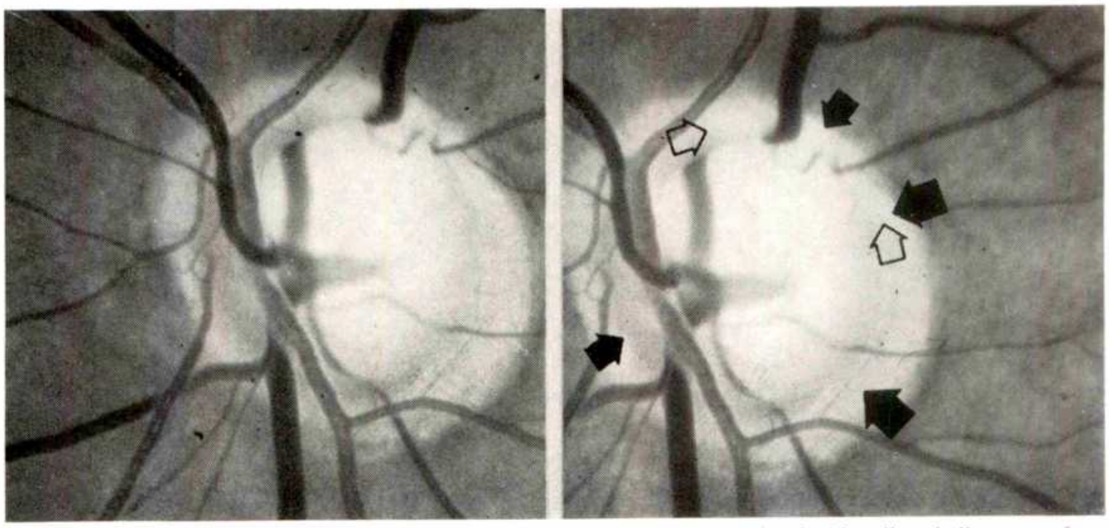

FIG. 3 *Cupping with pallor of the neuroretinal rim; glaucomatous cupping associated with pallor of all or part of neuroretinal rim. In this example neuroretinal rim (black arrows) has to be differentiated from adjacent peripapillary atrophy. Pallor of neuroretinal rim may be seen in one segment (hollow arrows)*

relatively undeviated course across the disc surface, apparently unsupported by disc tissue (this characteristic of retinal vessels 'bridging' an optic cup resembles the 'flyovers', or overpasses at road junctions, hence the name). On direct ophthalmoscopic examination, the optic cup with overpass cupping did not appear particularly enlarged as a major uniocular clue to the size of the optic cup is displacement of retinal vessels. The true size of the optic cup was only apparent on stereoscopic examination. This type of tissue loss (overpass cupping) was considered as a separate class.

Cupping without pallor of the neuroretinal rim

An optic disc with a pinkish neuroretinal rim but

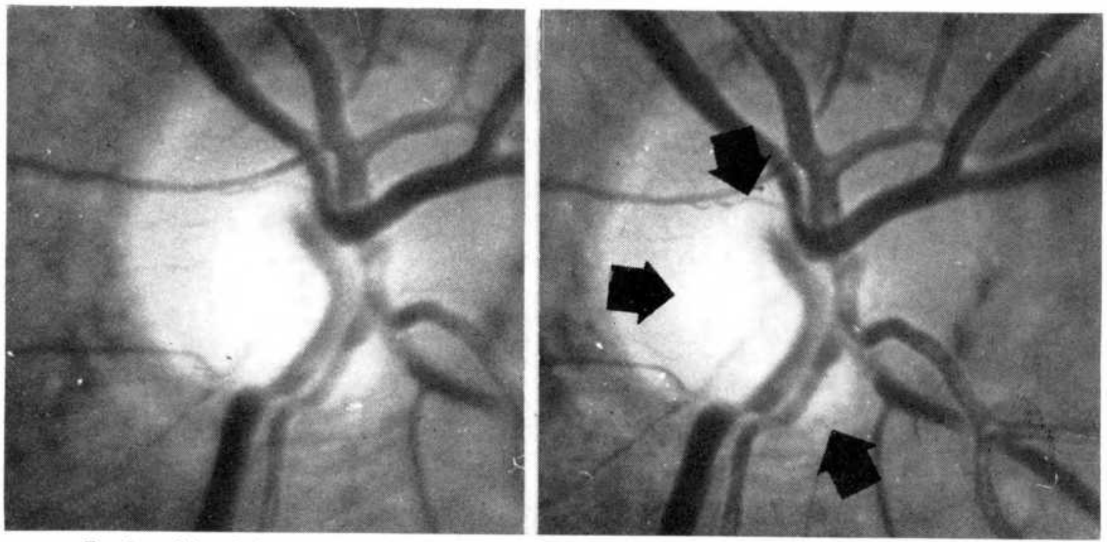

FIG. 4 *Focal notching of the neuroretinal rim; neuroretinal rim is very thin in one localized segment. This is associated with localized enlargement of optic cup (arrowed). There is no evidence elsewhere on optic disc of enlargement of optic cup*

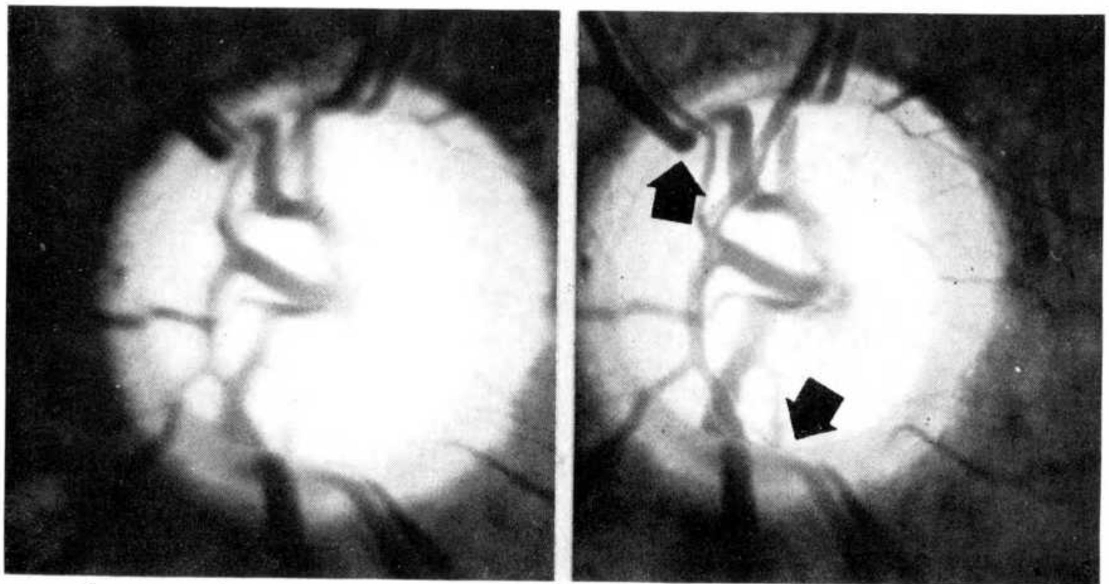

FIG. 5 *Bean-pot cupping; enormous size of optic cup, together with posterior bowing of laminar cribrosa and undermining of the neuroretinal rim resembles a 'bean pot' or gourd. Undermining of neuroretinal rim is emphasized by the retinal vessels 'disappearing' behind the rim for part of their course (arrows)*

with apparent enlargement of the optic cup was considered to have cupping without pallor of the neuroretinal rim. The pertinent clues were marked thinning of the neuroretinal rim together with steeply-sided walls to the optic cup and sharply angulated vessels, resulting in an oval cup out of proportion to that expected from the shape of the optic disc (Portnoy, 1973). This appearance was in some cases considered distinctive enough to indicate acquired glaucomatous cupping. In other cases the changes were less marked, evidence for glaucomatous cupping being obtained by comparison of the two optic discs from one subject. Here the following were taken as evidence for enlargement: asymmetry of the surface area of the cup (a difference of $\geqslant 0.2$ in the C/D ratio was considered significant); the steepness of the slope of the walls of the cup, or the depth of the cup. These signs, taken to indicate an acquired change, were most frequently noted at the infero-temporal part of the cup. The supero-temporal area was the next most frequently affected, while enlargement in other directions occurred less often.

Many of these optic discs could have been considered normal if examined individually without evaluation of the fellow disc. It was only by comparing the two discs that asymmetry became apparent.

Cupping with pallor of the neuroretinal rim

In certain optic discs, cupping was combined with pallor of the neuroretinal rim—that is reduced vascularity of the neuroretinal rim which affected part or all of its extent. Also present were those signs described that suggested enlargement of the optic cup and thinning of the neuroretinal rim secondary to raised intraocular pressure. The nerve fibre bundle layer was usually invisible.

Focal notching of the neuroretinal rim

In some eyes localized enlargement of the optic cup with thinning of the neuroretinal rim was present (notching), but *without* apparent cup enlargement elsewhere. This appearance was sufficiently distinctive to justify a separate category. In this series, the notch was usually in the infero-temporal quadrant. These eyes had the highest incidence of visible nerve fibre bundle defects.

Bean-pot cupping

Bean-pot cupping referred to the extreme enlargement of the optic cup already described. This occurred with or without pallor of the neuroretinal rim.

There was a general tendency for the two optic discs of any one patient to exhibit the same optic disc type. This was especially true for those cases with localized, or focal, notching and those with 'bean-pot' cupping. When the same optic disc types were not found, the following combinations occurred: normal + cupping with or without neuroretinal rim pallor; overpass + cupping with or without neuroretinal rim pallor.

Discussion

The proportional representation of each type in this series does not necessarily reflect the overall incidence in a glaucoma population. In the first place the population was highly selected because of the referral nature of the practice of one of us (GLS). Furthermore, only those patients with technically excellent photographs were chosen for analysis.

There appear to be distinct morphological disc types occurring in glaucomatous disease. Although clearly there was a definite overlap between groups, and some features were found common to more than one type it was still possible to classify the discs into five distinct morphological types. It was the predominant feature (overpass, bean-pot, etc.) which decided placement. Different optic disc types could have similar degrees of visual field loss and therefore be at the same stage of glaucomatous disease from the functional point of view (Hitchings and Spaeth, in preparation).

It is always slightly suspect to state that an individual optic cup has enlarged without documentation in a longitudinal study. The inference that such enlargement does occur is based on previous studies which reveal striking symmetry between the two discs in any one person (Fishman, 1970; Portnoy, 1973). Furthermore, there is evidence that the normal cup is horizontally oval or circular (Kirsch and Anderson, 1973; Weisman and others, 1973). Vertical ovality of the cup which exceeds that which could be explained on the basis of the vertical ovality of the disc itself suggests an acquired change (Kirsch and Anderson, 1973; Portnoy, 1973; Weisman and others, 1973).

An alternative explanation for an acquired enlargement of the optic cup is that it is age related. It seems likely that the optic cup may enlarge with age. Pickard (1948) noted this from a longitudinal study, while Schwartz, Reuling, and Garrison (1975) demonstrated an increase in the horizontal C/D ratio with age by examining stereophotographs of the optic disc. This is at variance with the earlier work of Armaly (1967) who felt, on the basis of uniocular ophthalmoscopy, that the optic cup did not increase with age. Although Schwartz and others (1975) did not specifically measure it, it seems possible that the vertical C/D ratio does not enlarge more than the horizontal C/D ratio.

The existence and extent of peripapillary pigment clumping was noted (Primrose, 1972), but the present study shows that it is not pathognomic for glaucoma as it was found in 27 cases (11 per cent) of normal discs and in nine of these it occurred in eyes that were considered clinically normal. However, in agreement with the finding of Wilensky and Kolker (1976) the incidence of pigmentary clumping rose considerably with glaucomatous disease, occurring in over 90 per cent of eyes with notching of the optic cup and bean-pot cupping. In addition, in cases with bilateral glaucomatous disease, the eye with the more advanced changes tended to show a greater amount of pigmentary clumping.

In those cases where it was possible to re-examine the patients with red-free light (Hoyt and others, 1973), we found that examination of stereophotographs for defects with nerve fibre layer appeared to be just as accurate. Care was taken to differentiate true from pseudo 'gutters'. All cases in this series with nerve fibre bundle defects had glaucomatous cupping. The nerve fibre layer could not be visualized at all in many patients with glaucoma, notwithstanding the presence of normal fields (on kinetic Goldmann field testing). Visibility was not improved with red-free light. There would appear to be a non-specific depression of light reflexes arising from this layer which is associated with, and possibly related to, raised intraocular pressure, and/or age.

The highest incidence of nerve fibre bundle defects was seen in cases with localized notching of the neuroretinal rim. There was always a corresponding 'dense' field defect on Goldmann perimetry, in marked distinction from discs in other groups where it could be difficult to state whether a field defect was present at all. In the group of eyes with cupping without neuroretinal rim pallor, it was possible to detect changes in the appearance of the optic nerve that suggested glaucoma, *before* nerve fibre bundle defects could be seen. It appeared that visualization of the nerve fibre layer was a valuable guide when present. That it could not be seen in many cases, despite full fields, suggests its value in diagnosis is limited.

The variable appearance of the optic nerve in glaucoma suggests a different response of the nerve to differing disease processes. This may reflect anatomical differences between optic nerves, variation in the duration of the height of the raised intraocular pressure and coexistence of cardiovascular and haematological disease. These factors may act singly or in varying combinations. This is borne out to some extent by our knowledge of the natural course of glaucomatous disease. Children and young adults are known to develop glaucomatous cupping and visual field loss after a comparatively short time. The flame-shaped haemorrhage may indicate sudden visual field loss (Drance and Begg, 1970). Conversely some nerves appear capable of withstanding many years of increased intraocular pressure without damage. The appearance of the glaucomatous disc may be affected by many factors. Recognition of differing morphological types may be a step towards recognizing the predominating factors in each case.

Summary

Five different descriptive types of glaucomatous optic discs are described, based on the examination of ×2 magnification stereophotographs of 252 patients from the files of the Glaucoma Service at Wills Eye Hospital. The method of analysis is described in detail. These types include: overpass cupping, cupping without pallor of the neuroretinal rim, cupping with pallor of the neuroretinal rim, focal notching of the neuroretinal rim, and bean-pot cupping.

These morphological types may be caused by variations in factors contributing to the pathogenesis of glaucomatous eyes. Recognition of these differing types may help in determining the factors in each case.

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Plasma cortisol suppression response in the South African Black population with glaucoma

JEFFREY FREEDMAN, ROBERT DAVID, L. ANDRE VAN DER WALT, AND MAURICE H. LUNTZ
From the Glaucoma Clinic, St John Eye Hospital, Baragwanath, South Africa

Results of a plasma cortisol suppression test have never been reported in a Black glaucoma population, although there have been reports of tests carried out on glaucomatous patients generally. The results have varied from marked suppression in glaucomatous patients (Becker, Podos, Assef, and Cooper, 1973; Rosenberg and Levene, 1974) to no suppression at all (Schwartz and Levene, 1972).

Glaucoma of all types is prevalent in the South African Bantu (Luntz, 1973). All the patients in this study were seen at the Glaucoma Clinic, St John Eye Hospital, Baragwanath.

Material and methods

Twenty-five glaucomatous patients were tested and classified according to their age and sex, and type of glaucoma (Table I). A matching group of 19 patients awaiting cataract surgery or corneal grafts were also tested and classified according to their age and sex (Table II). None of the patients had diabetes nor had any been treated with corticosteroids before participation in the trial.

An initial serum cortisol level was estimated between 7.30 and 8.30 a.m., the time at which blood cortisol concentration is highest (Murphy, Engelberg, and Patte, 1963). Patients in both groups were given 15 mg prednisone orally, in three divided doses of 5 mg each one, five, and nine hours after the initial blood tests had been taken. Again at 7.30 and 8.30 the following morning, serum cortisol levels were tested.

Peripheral serum levels of cortisol were determined employing a standard competitive protein binding radioassay. Results were computer-derived using a probit-log transformation plot on a weighted regression line. Reference sera were obtained from Nuclear Medical Systems; these served as controls.

Results

The serum cortisol level in the control group before and after administration of the oral corticosteroid is given in Table III. The normal level of cortisol before administration varied from a low of 6·3 μg/100 ml to a high of 24·9 μg/100 ml, this being within the normal range at 8 a.m. (Murphy, 1967). The average initial serum cortisol level in the control group was 13·4 μg/100 ml.

In 13 of the control patients the blood cortisol level decreased after administration of prednisone, while in six patients there was no decrease or even a minimal increase. The average level of cortisol after administration of prednisone in this group was 10·9 μg/100 ml. This represents an average decrease of 2·5 μg/100 ml in the plasma cortisol level of the control group after the orally administered corticosteroid.

The serum cortisol levels before and after cortisol suppression in the glaucomatous patients are shown in Table IV. The average initial cortisol level was

Table I *Age, sex, and type of glaucoma (25 patients)*

Age range (years)	*Glaucoma*					
	Primary open-angle		*Pseudocapsular exfoliation*		*Chronic angle-closure*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
40–50	3	—	—	—	2	1
50–60	3	1	2	1	1	—
60–70	2	1	5	—	—	—
>70	—	1	1	—	1	—
Total	8	3	8	1	4	1

Table II 19 *control subjects*

Age range (years)	*Men*	*Women*
40–50	3	3
50–60	2	3
60–70	2	4
>70	2	—
Total	9	10

Address for reprints: J. Freedman, FRCS, Department of Ophthalmology, University of Witwatersrand, Hospital Street, Johannesburg 2001, South Africa

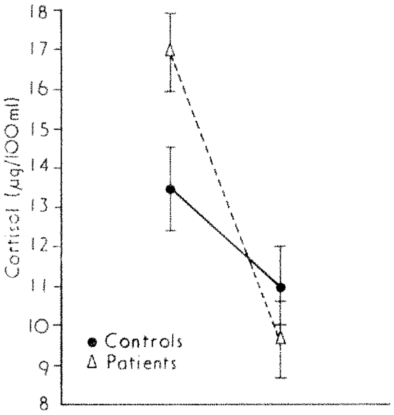
Table III *Plasma cortisol levels in* 19 *control patients* (µg/100 *ml) before and after administration of oral cortisone*

Under 60 *years*										
Plasma cortisol level										
Before cortisone	15·4	14·0	9·4	6·9	13·5	10·7	8·7	15·9	13·3	19·9
After cortisone	10·7	14·6	10·7	6·7	12·6	6·5	3·7	10·7	17·5	15·5
Over 60 *years*										
Before cortisone	6·3	13·8	11·6	13·9	11·6	10·3	24·9	14·0	20·7	
After cortisone	4·3	17·4	12·2	7·9	11·0	5·7	16·3	12·9	5·0	

Table IV *Plasma cortisol levels in* 25 *glaucomatous patients* (µg/100 *ml) before and after administration of oral cortisone*

Age (years)	*Plasma cortisol level* *Before cortisone*	*After cortisone*
Primary open-angle glaucoma		
42	20·0	12·8
48	9·3	3·7
49	24·9	16·4
50	13·7	3·3
55	23·3	13·9
57	12·1	3·7
60	21·8	18·9
62	13·6	13·1
64	13·0	5·2
65	21·2	17·8
73	17·6	4·2
Open-angle glaucoma and pseudocapsular exfoliation		
50	21·4	16·9
56	14·8	3·1
58	17·5	9·2
60	11·0	12·2
65	25·6	16·9
66	14·2	11·1
68	17·1	3·7
70	20·0	13·1
72	18·7	5·3
Chronic angle-closure glaucoma		
41	15·0	11·1
42	9·7	3·2
42	18·2	5·3
53	24·6	15·3
72	4·4	4·5

16·9 µg/100 ml and the postsuppression level averaged 9·7 µg/100 ml. In 23 out of the 25 patients the plasma cortisol level decreased after orally-administered corticosteroids and only two patients maintained a steady level. The average decrease resulting from the administration of prednisone in the glaucomatous patients was 6·8 µg/100 ml (Table IV and Figure).



The cortisol suppression response showed no significant differences among the different types of glaucoma, Table IV.

Discussion

There are reports in the literature concerning the response of glaucomatous patients to systemic corticosteroid administration. There is no uniformity in the reported results. Schwartz and Levene (1972) in one study, and Weinstein and Mori (1972) working independently, found that the initial cortisol levels in glaucomatous patients were higher than in a control group. Furthermore, Schwartz and Levene (1972) found that glaucomatous patients behaved like patients with Cushing's syndrome and did not respond by lowering their serum cortisol levels after administration of oral corticosteroids. Becker and others (1973), however, found that in their glaucomatous patients, oral cortisone administration caused a marked lowering of the plasma cortisol level, that is, their glaucomatous patients were highly sensitive to the cortisol suppression test.

In a more recent publication, Rosenberg and Levene (1974) supported Becker's earlier finding, and reported a significant reduction in plasma cortisol levels in their glaucomatous patients compared with normal subjects after oral administration of corticosteroids.

We found that the initial serum cortisol level was higher in glaucomatous patients compared with a control group (16·9 µg/100 ml compared with 13·4 µg/100 ml). This finding correlates with those quoted by Weinstein and Mori (1972) and Schwartz and Levene (1972) for White patients.

The suppression of plasma cortisol levels after orally-administered cortisone was more marked in glaucomatous patients than in the control group, an average decrease by 7·0 µg/100 ml in glaucomatous patients and only 2·5 µg/100 ml in the control group. Becker and others (1973) and Rosenberg and Levene (1974) reported similar findings.

According to Levene and Schwartz (1968), people in whom the intraocular pressure rises in response to the topical administration of corticosteroids, behave like patients with Cushing's syndrome as far as their response to systemic administration of corticosteroids is concerned. Therefore, the glaucomatous patients who responded markedly to the cortisol suppression test should not be topical corticosteroid responders. The response to topical corticosteroids could not be measured in the patients in our study as they all had advanced glaucoma and were on full medical treatment.

In this group of Black patients, therefore, a definite reduction of plasma cortisol levels indicates that corticosteroid suppression occurred both in the control subjects and the glaucomatous patients. The difference between cortisol levels in control and glaucomatous patients before initiation of the test dose of cortisone is significant to a 99 per cent confidence limit. There was no statistical difference between the final suppressed levels of both groups (10·9 µg/100 ml as compared with 9·9 g per cent), see Figure.

However, the fall in the level of the plasma cortisol is the result of suppression which varied significantly ($P > 0{\cdot}001$) when comparing glaucomatous patients with the controls (Figure).

Summary

Plasma cortisol suppression was measured in 25 Black glaucomatous patients and in 19 Black patients of similar age and sex, but without glaucoma, who acted as controls. Initial serum cortisol levels were found to be slightly higher in the glaucomatous group. The response to systemically-administered cortisone was statistically more marked in the glaucomatous patients compared with the control group.

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Atenolol versus propranolol
A comparison of ocular hypotensive effect of an oral dose

MARGARET J. MACDONALD, PATRICIA M. CULLEN AND
CALBERT I. PHILLIPS
From the Department of Ophthalmology, University of Edinburgh, and Princess Alexandra Eye Pavilion, Edinburgh

Both atenolol and propranolol by mouth reduce ocular tension in normal and glaucomatous eyes (Phillips, Howitt, and Rowlands, 1967; Elliot, Cullen, and Phillips, 1975; Wettrell and Pandolfi, 1975). These drugs are β-adrenergic blockers but propranolol affects both β_1 and β_2 receptors (as well as having a 'membrane' effect), while atenolol is a more specific β_1 receptor antagonist and lacks the membrane-stabilizing activity of propranolol.

Aims

The aim of this study was to compare the ocular hypotensive actions of single oral equipotent doses of atenolol (50 mg) and propranolol (40 mg) in a double-blind cross-over study on 10 patients.

Selection of patients

The 10 individuals were chosen from patients attending glaucoma clinics; they comprised six with open-angle glaucoma, three with chronic closed-angle glaucoma, and one with ocular hypertension. They all satisfied previously-established criteria regarding age and general health—namely, they were aged 70 years or less and had no evidence of cardiorespiratory disease or diabetes, and had normal renal function. Only one eye from each patient, chosen at random, was included in the study.

Details of the patients including previous treatment to the eye examined are given in Table I.

Methods

Conditions were standardized as far as possible. Local treatment to the eye to be examined and systemic carbonic anhydrase inhibitors were stopped 24 hours before test days. Patients attended as outpatients between 9.0 a.m. and 4 p.m. with at least a week between test days. After initial applanation tonometry on the eye randomly selected for examination, the blood pressure and pulse rate were measured and either 50 mg of atenolol or 40 mg of propranolol was given by mouth. The observers were unaware of which treatment was given and the order of administration was randomized. The same three properties were measured at hourly intervals for seven hours thereafter, by the same examiners. The same procedure was carried out on the second test day with cross-over of the drugs; five patients (at random) had atenolol first and propranolol second, while the other five had the drugs in the reverse order.

Table I *Details of patients*

Patient	*Sex*	*Age (years)*	*Diagnosis*	*Previous treatment*
1	Male	66	Open-angle glaucoma	Pilocarpine
2	Male	65	Chronic closed-angle glaucoma	Peripheral iridectomy pilocarpine
3	Female	48	Open-angle glaucoma	Pilocarpine dichlorphenamide
4	Female	70	Open-angle glaucoma	Pilocarpine
5	Male	62	Open-angle glaucoma (aphakic)	Cyclodialysis pilocarpine
6	Male	52	Chronic closed-angle glaucoma	Sector iridectomy pilocarpine
7	Male	62	Ocular hypertension	Nil
8	Male	62	Open-angle glaucoma	Trephine pilocarpine adrenaline
9	Male	67	Chronic closed-angle glaucoma	Iris inclusion
10	Female	68	Open-angle glaucoma	Pilocarpine

Results

OCULAR TENSION

In all 10 patients ocular tension fell after both atenolol and propranolol. For both treatments a significant reduction in mean tensions occurred two hours after administration and was maintained after seven hours. However, at all times the mean fall in ocular tension was greater during treatment with atenolol compared with propranolol, and with the exception of the sixth-hourly reading, these differences were statistically significant, whether or not allowance was made for the slightly different

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Table II *Comparison of ocular hypotensive effects of atenolol and propranolol based on adjusted mean intraocular pressure in 10 patients*

	Hours after treatment							
	0	1	2	3	4	5	6	7
Propranolol								
Means	27·2	26·3	20·7	20·1	18·3	16·7	18·2	19·6
Adjusted Means		25·8	20·2	20·1	18·0	16·6	18·2	19·7
Atenolol								
Means	25·3	22·1	16·7	17·0	15·5	14·7	15·9	16·7
Adjusted Means		22·6	17·2	17·0	15·8	14·8	15·9	16·6
Difference between adjusted means		3·2	3·0	3·1	2·2	1·8	2·3	3·1
SE of difference		0·80	1·12	0·70	0·72	0·74	1·20	0·88
Significance (P)		<0·01	<0·05	<0·01	<0·05	<0·05	NS	<0·05

NS—Not significant

'Adjusted means' have been adjusted for the covariate (pre-dose pressure)

mean starting pressures before the drops were given (Table II).

BLOOD PRESSURE AND PULSE RATE

There was no reduction in diastolic blood pressure after either drug but there were significant falls in systolic pressure 2, 4, 5, and 6 hours after propranolol and three hours after atenolol.

Two hours after treatment by both drugs there was a significant reduction in pulse rate. This fall was greater with propranolol but the difference was not statistically significant.

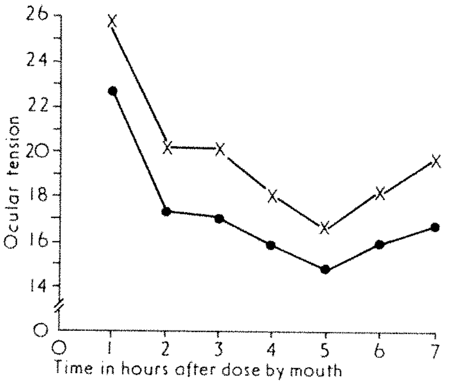

FIGURE *Graph showing greater effect on ocular tension of 50 mg atenolol than 40 mg propranolol. Each point represents mean of 10 patients. Means have been 'adjusted' to allow for different starting pressures. All except 'six hour' means were significantly different*

● = atenolol × = propranolol

Discussion

Two papers have shown the efficacy of systemic atenolol in reducing ocular tension after a single dose (Elliot and others, 1975), and during a period of eight days (Wettrell and Pandolfi, 1975) which confirms that β-adrenergic blockade or, more specifically, β_1 blockade, can produce a net effect of reduction in intraocular pressure. These observations suggest that the membrane-stabilizing effect of propranolol is of negligible importance in lowering intraocular pressure because atenolol 50 mg is more potent than 40 mg propranolol in glaucomatous eyes. This conclusion is supported because Wettrell and Pandolfi (1975) found no significant difference in the ocular hypotensive effect on *normal* eyes of these two drugs which they gave in the above doses twice daily for eight days. This conclusion was predictable from the much greater efficacy of racemic propranolol (that is, a mixture of the dextro- and laevo-rotary form) than dextro-propranolol since the former has 60× the β-blocking potency of the latter but the same effect on membrane stability (Vale and Phillips, 1970).

We have no satisfactory explanation for this unexpected effect on intraocular pressure of β-blockers which has been discussed at some length in the papers already mentioned. It would be biologically consistent if adrenergic stimulation increased outflow commensurately with increased inflow to maintain a steady state. Route of administration may therefore be important—local application affecting outflow and systemic application inflow. Although we suspect that β-blockers given systemically reduce production of aqueous humour, the efficacy of propranolol (as well as practolol) in the form of eye drops (Vale and Phillips, 1973) suggests that an improvement in outflow may also take place. It will be interesting to observe the effect of atenolol eye drops when they become available, not only for theoretical reasons but also because, if the expected fall in pressure is confirmed, a β-blocking drug suitable for local administration may become available in clinical management of glaucoma.

Summary

In a controlled double-blind cross-over trial in 10 patients comprising six with open-angle glaucoma, three with closed-angle glaucoma, and one with ocular hypertension, a single oral dose of atenolol (50 mg) was significantly more effective than propranolol (40 mg) in reducing ocular tension.

We are grateful to ICI (Pharmaceuticals) Ltd, for supplies of atenolol (Tenormin ICI) and propranolol, and to Dr A. Rushton for information and discussion.

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Brit. J. Ophthal. (1976) 60, 792

Book reviews

The Eye (Structure and Function in Disease Monograph Series). By G. K. KLINTWORTH and M. B. LANDERS, III. 1976. Pp. 236, figs, tables, refs. Williams & Wilkins, Baltimore ($16·50)

The correlation of clinical conditions with pathological changes is essential for the proper understanding of diseases of the eye. This monograph, compiled from lectures on ophthalmic pathology to medical students, explains this clearly and precisely. There are as many clinical illustrations as pathological, and both types are simple and of good quality. There are no electron micrographs nor is electron micrography mentioned.

Modern concepts on immunology are clearly explained and metabolic diseases are particularly well described, with explanations of their histochemistry and a table giving the types of inherited disease. The important subjects of retinal disease and cataract are relegated to the last chapter on miscellaneous conditions and might have been included earlier. The place of fluorescein angiography, now so important in diseases of the retina, is insufficiently stressed.

The text is almost free of errors ('opthalmic pathology' in the foreword is an exception) and the quality of production is excellent. The book is a splendid introduction to ophthalmic pathology and will be useful to those beginning to study the specialty whether at undergraduate or postgraduate level. C. A. BROWN

The Intraocular Lens in Perspective. Edited by D. M. WORTHEN and P. S. BINDER. 1976. Pp. 142, 23 figs, refs. Stratton, New York ($14·95)

This slight publication comprises a selection of the papers delivered to, and the panel discussion arising from, a symposium of the same title, conducted by the Division of Ophthalmology at the University of California in San Diego, 1975.

Despite the best endeavours of the editors it suffers from the lack of continuity commonly associated with published symposia and so falls short of the standards which the title leads one to expect. The perspective is sadly incomplete, and it is necessary to point out that there are no controls for the statistics produced by many of the contributors. There are, however, some most useful tips to be gleaned from the contributions of several surgeons experienced in this method of correction of aphakia which those interested in this field may find of value. A. D. MCG. STEELE

Modern Problems in Ophthalmology: Ocular Immune Responses, vol. 16. Edited by W. BOKE and M. H. LUNTZ. 1975. Pp. 333, figs, tables. Karger, Basel (US$38·25)

As with the previous volumes in this series, volume 16 is based on papers presented at an international meeting in Strasbourg (1974). It deals mainly with pathogenic immune reactions in ocular tissues of experimental animals. The book is divided into five chapters and is concerned with retinal antigens and their role in ocular inflammation, viral and parasitic immunopathology, and laboratory investigations in uveitis. The last chapter deals with immunosuppressive treatment.

There is no doubt this book contains much information of great interest to many experimental ophthalmologists and those interested in the fast growing field of ocular immunology. Newcomers who intend entering this field will find it to their advantage to read these collected papers which are also a good source for references. It is difficult, however, to justify the price and I can only hope that all ophthalmic libraries and research institutions will buy this book because it is otherwise beyond the price most ophthalmologists can afford. A. H. S. RAHI

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At the next meeting of the International Society of Geographic Ophthalmology there will be symposia on the geographical distribution of ocular viral diseases and congenital ocular disorders. Free papers concerned with geographical ophthalmology will also be presented. Further details may be obtained from Dr E. E. Cass, Box 688, Fort Smith, NWT, XOE OPO, Canada.

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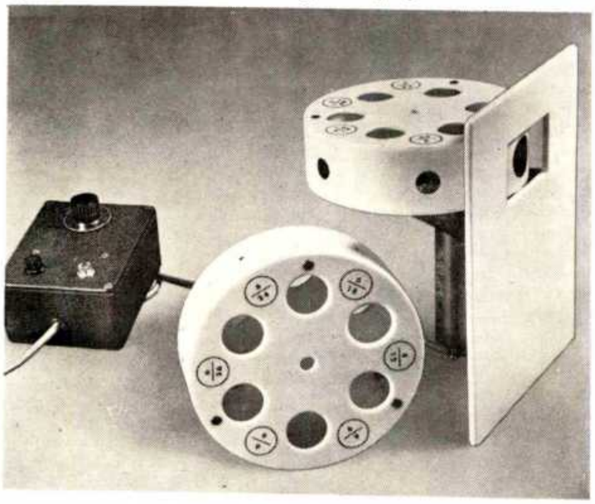

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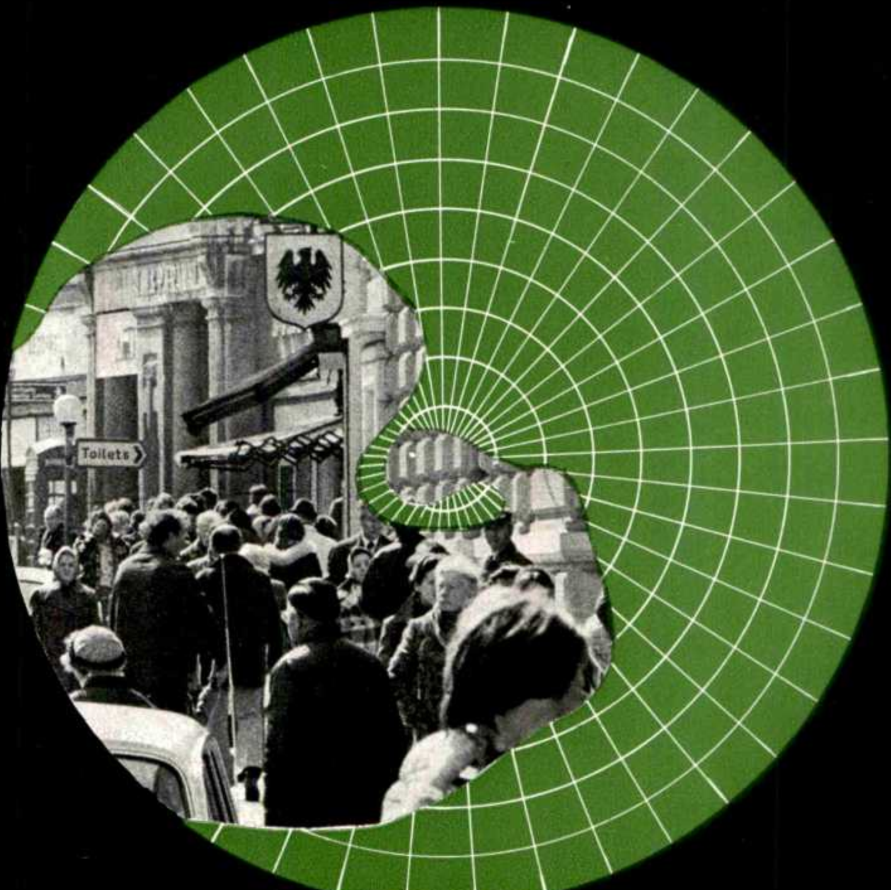

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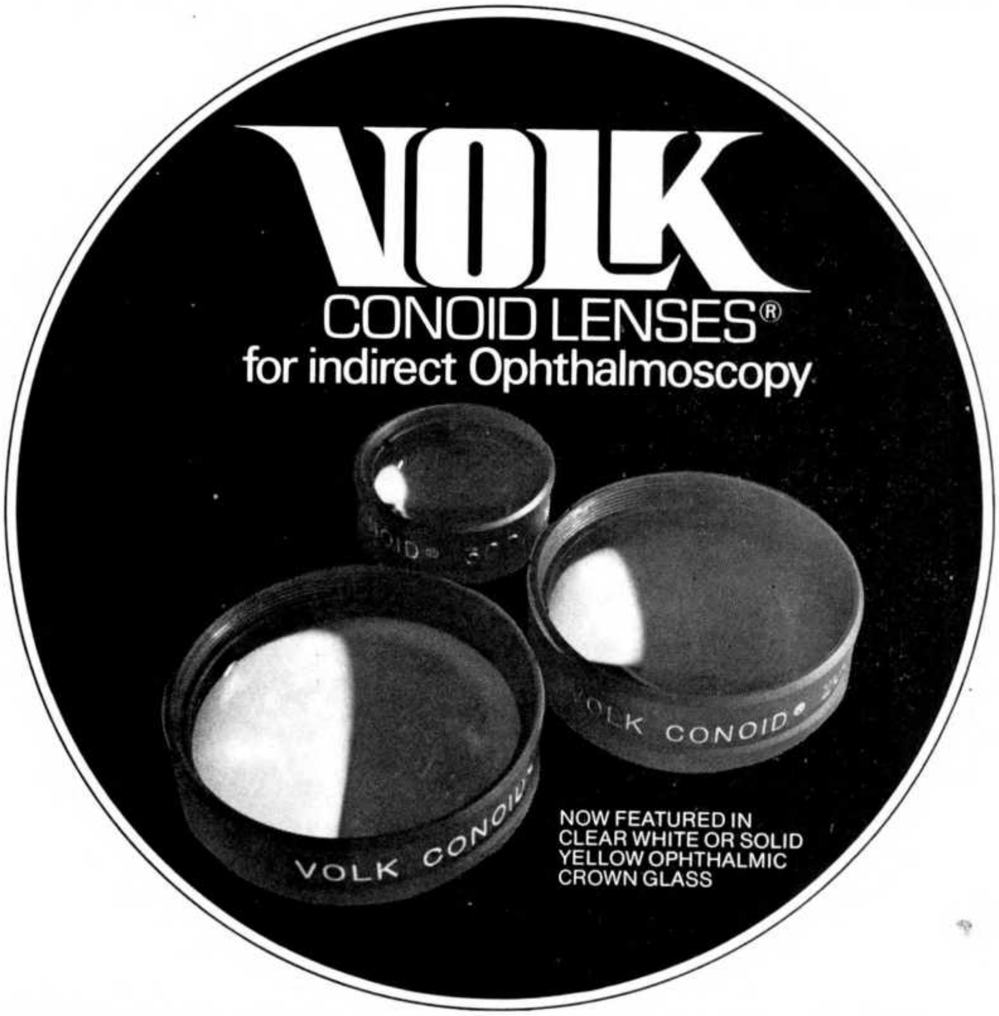
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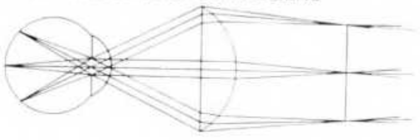

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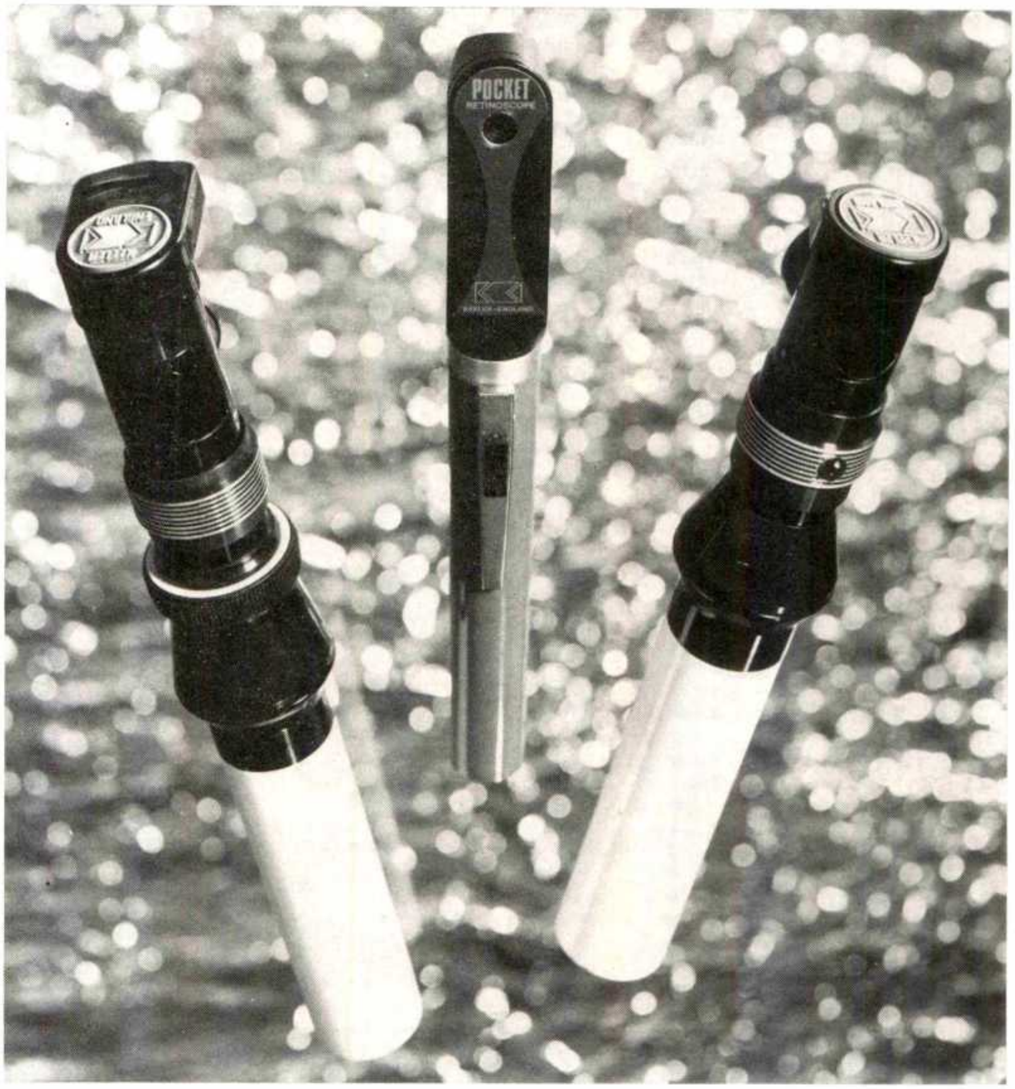

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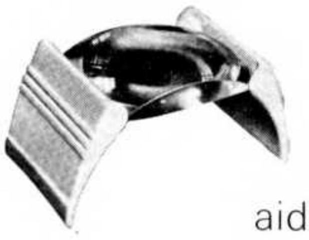

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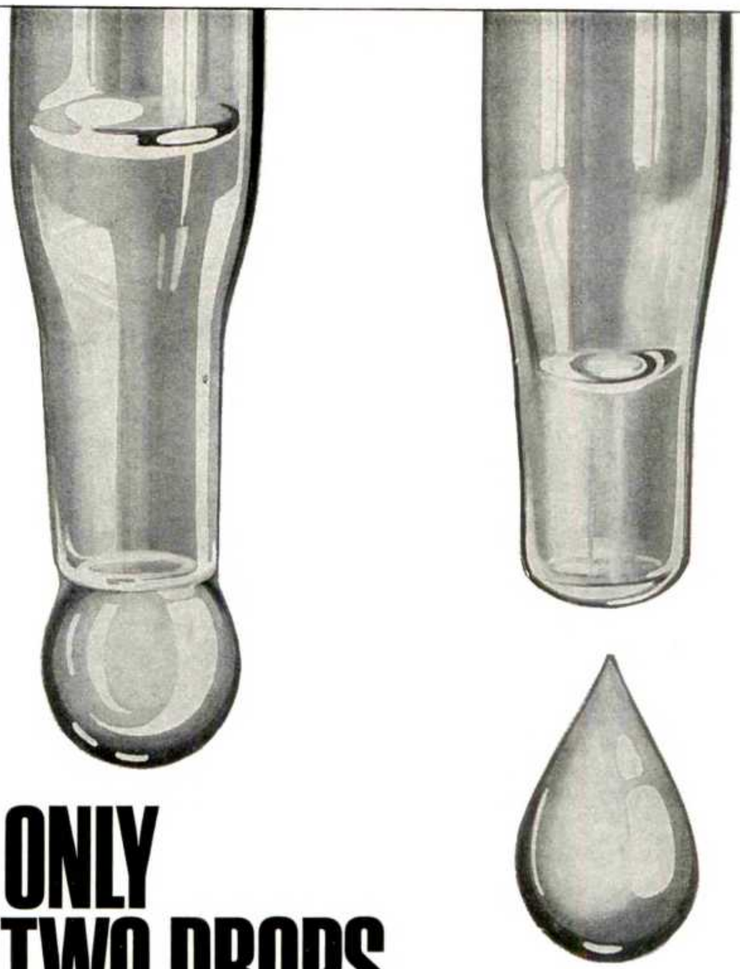

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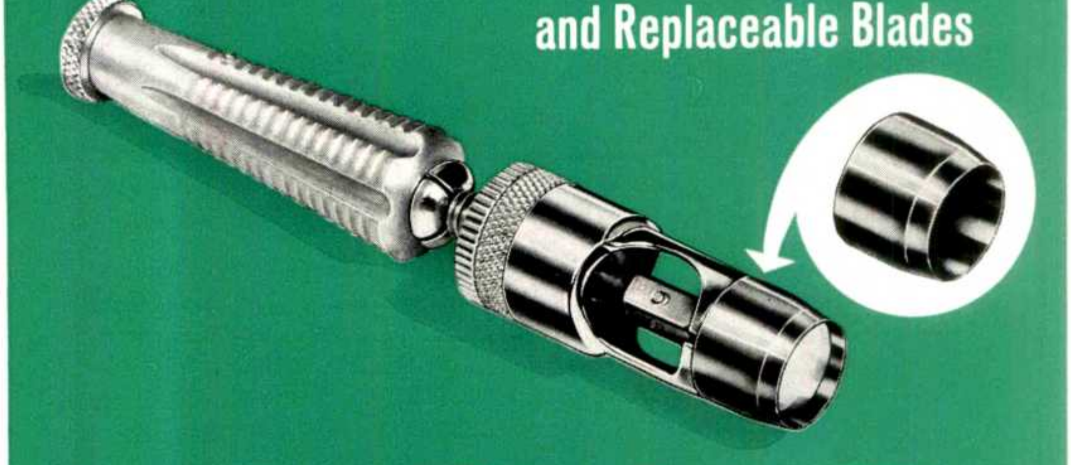

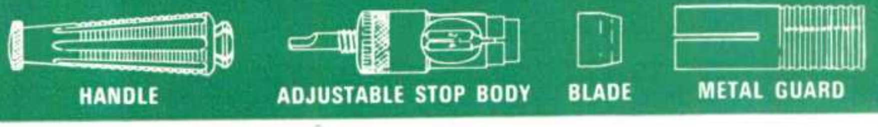

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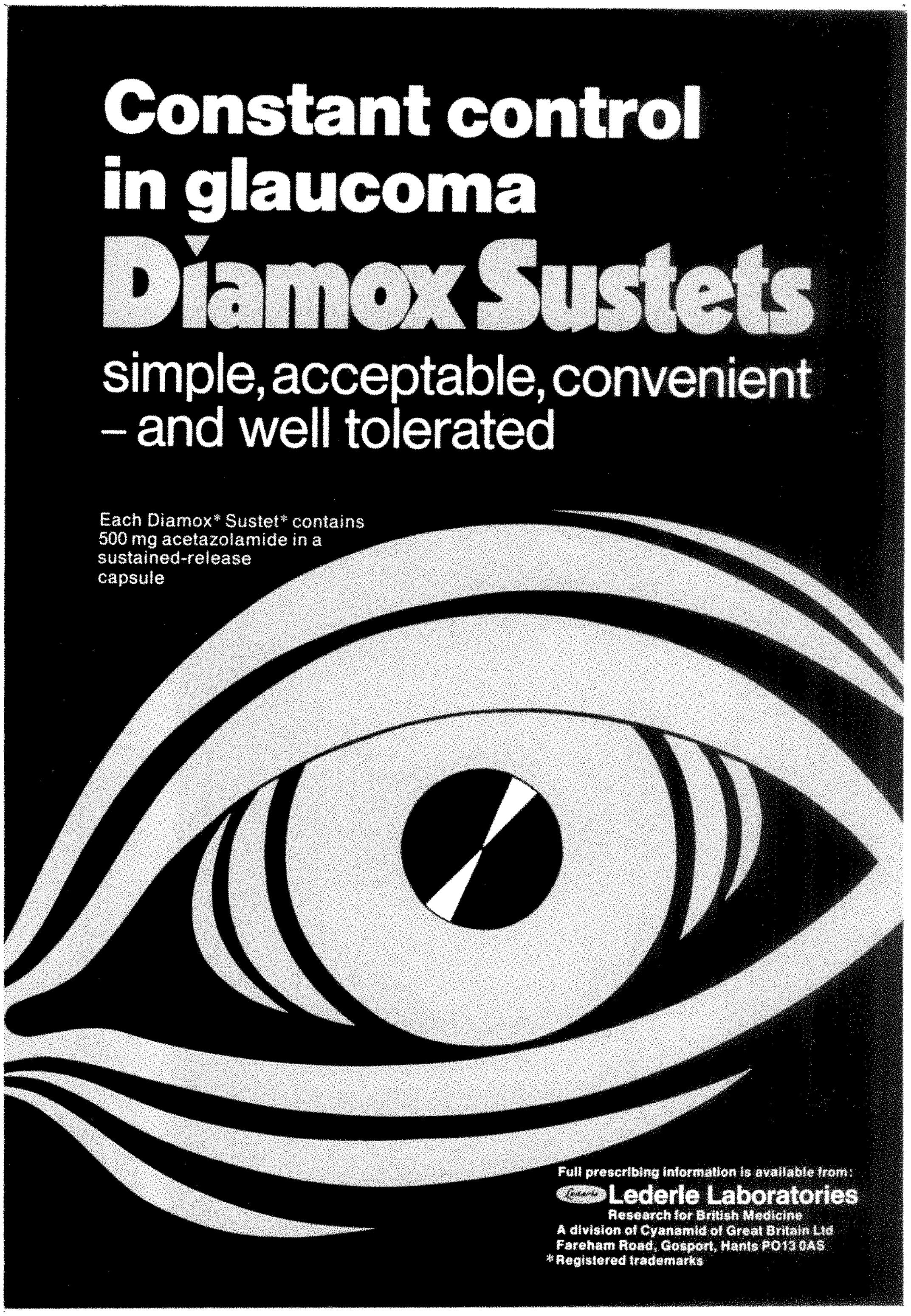

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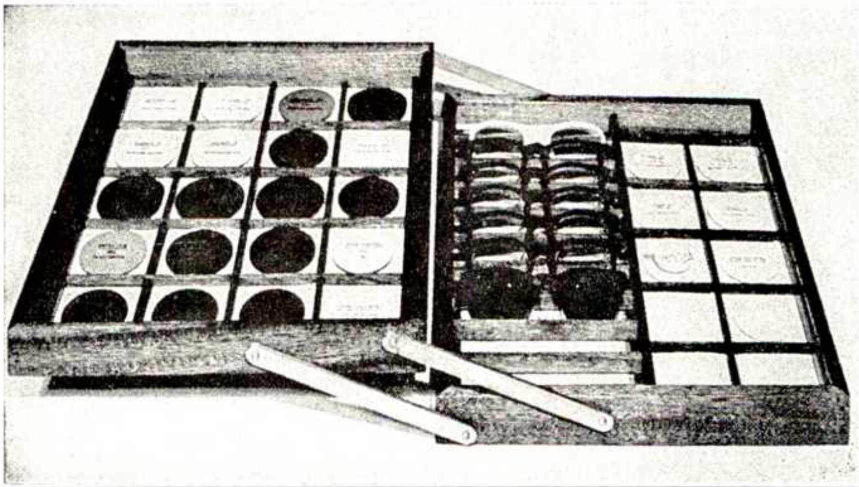

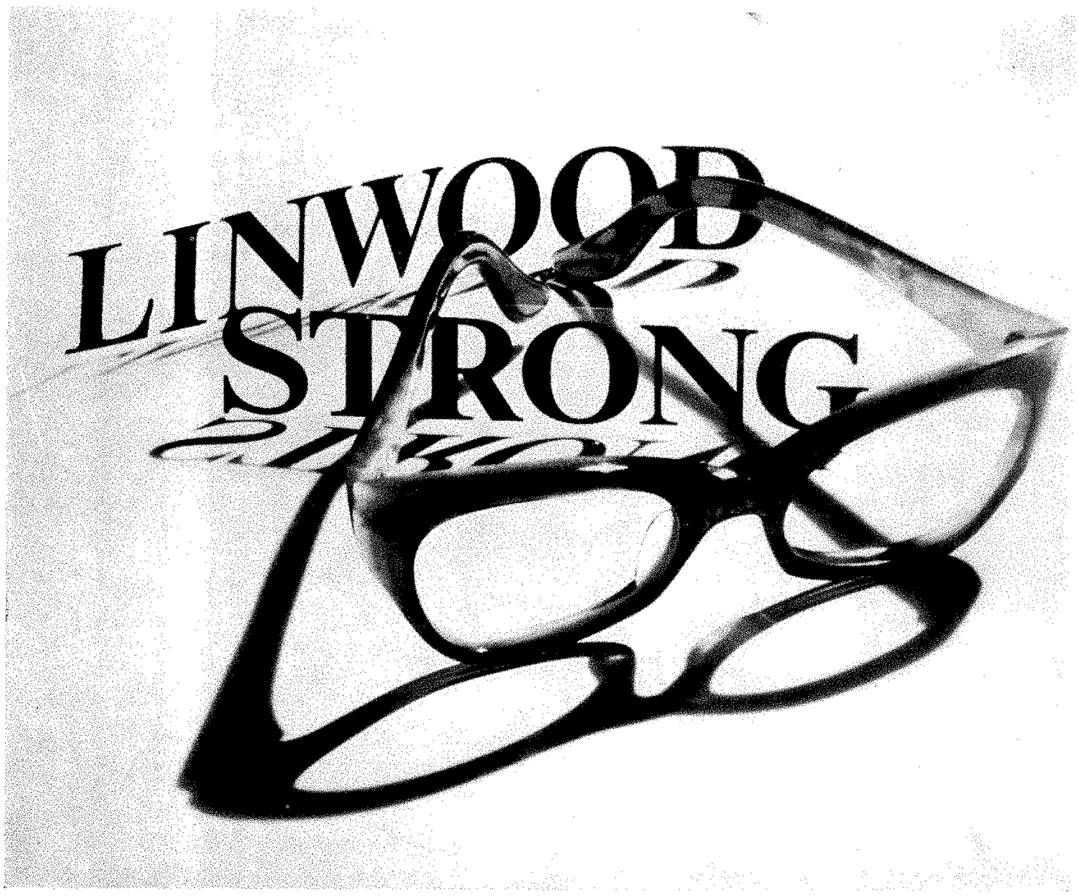

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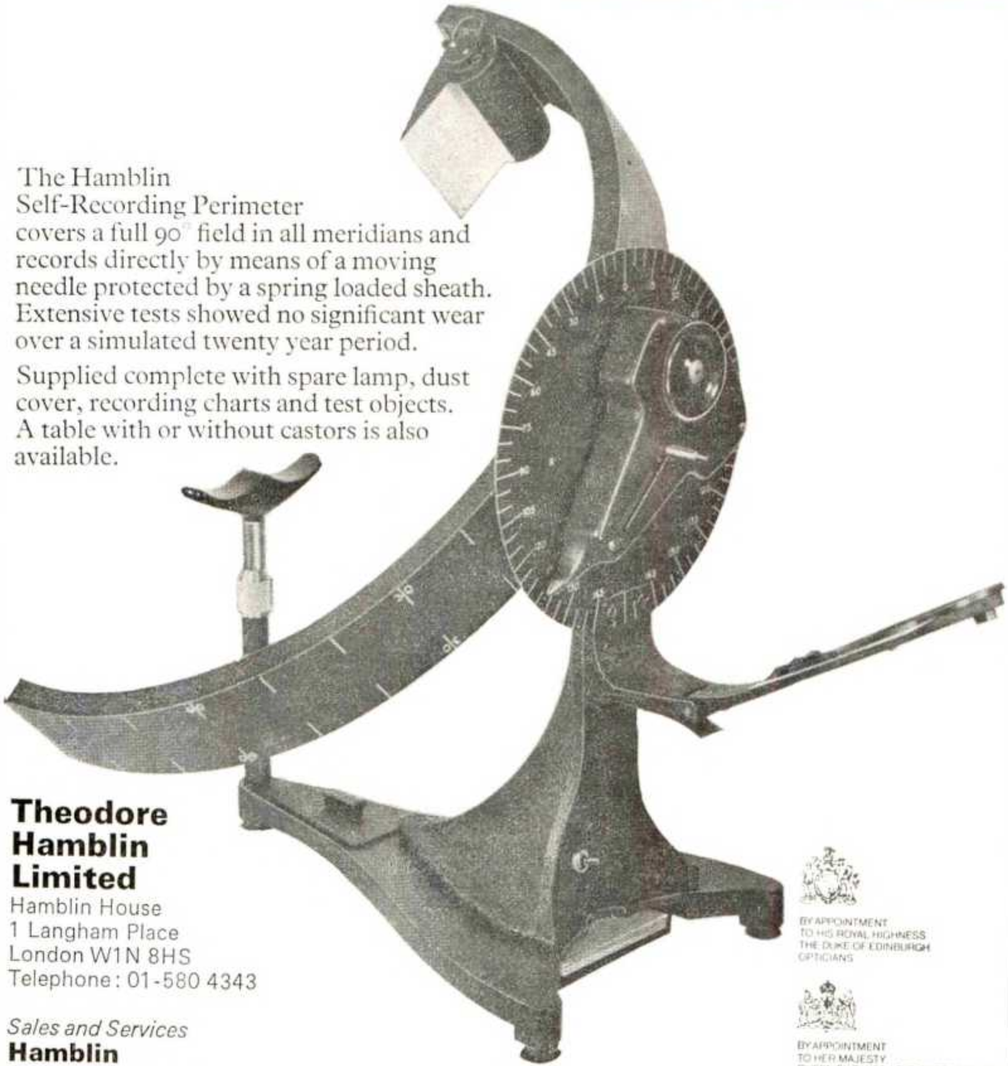

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Brit. J. Ophthal. (1976) **60**, 793

Editorial: Treatment of eyelid tumours

At one time the treatment of cancer was vested more or less exclusively in the hands of the surgeon —if no recognition is made of the rather meaningless and sometimes bizarre treatments which were provided by certain medical practitioners and which had no significant influence on the progress of the disease—although, it must be recognized that a profound personal interest in a patient afflicted by a devastating disease may provide a remarkable boost to the morale, despite the absence of any rational basis for the particular treatment. The advent of irradiation as a treatment for malignant disease marked an important step forward, but inevitably there was a considerable conflict between the surgeon (who had an established role in the treatment of cancer) and the radiotherapist (who was striving for such recognition). It is, of course, essential in putting forward a new doctrine to emphasize its importance, and this almost certainly applied to radiotherapy in the early days. However, the passage of time is a remarkable natural healer of conflict, and this is shown by the numerous multidiscipline clinics which have gradually developed over the years with involvement by the surgeon, radiotherapist, chemotherapist, and the pathologist who is no longer in isolation but concerned in correlating the clinical and histological features of the disease and particularly in recognizing certain characteristics which provide some clue to the likely progress of the disease and even the possible response to treatment.

This recognition of an interdependence of different disciplines is of significance and in the management of many forms of malignant disease there is a clear recognition of the role of each different form of therapy. For example, in breast cancer radiotherapy usually follows surgical treatment, whereas in certain forms of malignant disease of the bladder or naso-pharynx, irradiation is carried out sometimes before surgery. In certain other conditions the various roles are slightly less defined—such as in the craniopharyngiomas—when some neurosurgeons limit their treatment to the immediate relief of pressure by dealing with the cystic part of the tumour, particularly if the tumour is adjacent to the optic chiasma or the associated parts of the afferent visual pathways, so that the final resolution of the tumour is the province of the radiotherapist, whereas other neurosurgeons may feel impelled to attempt to eradicate the tumour irrespective of its extent.

In certain situations, however, there seem to be no clear guidelines regarding the treatment of cancer, and this certainly applies to tumours involving the eyelids, as illustrated in the two papers in this issue dealing with the same condition; in one the treatment is surgical whereas in the other it is irradiation. This must inevitably lead to confusion in the person who is confronted by such a case and yet has only a limited personal experience of the problem.

It is obviously not possible in an editorial to resolve such a situation, but it is reasonable to try to define the scope of the problem. There is little doubt that irradiation is an effective procedure in most tumours of the eyelids, provided it is carried out in a sufficiently thorough manner and provided the radiotherapist is aware of the damage to the eye which may result indirectly from the treatment so that every effort is made to avoid any complications by local measures—such as, by the use sometimes of a haptic contact lens. There is also little doubt that surgical treatment is effective but there are two important provisos: the surgeon must have a deep understanding of cancer so that the operation is planned to deal with the full extent of the possible spread of the disease and this demands that the niceties of surgical technique are entirely secondary to the consideration of the eradication of the tumour; and, the surgeon must have sufficient experience to be able to restore an adequate functioning eyelid, which is sometimes difficult particularly in the upper eyelid when there has been extensive disease, otherwise there is the long-term problem of exposure of the eye quite apart from the cosmetic defect.

There is one feature which predominates over all others in the conflicting claims of the surgeon and of the radiotherapist to deal independently with tumours of the eyelid; the person who advocates a particular method must have the knowledge and experience to stand a reasonable chance of effecting a cure because the problems of a recurrence after either method of treatment are likely to be formidable.

Brit. J. Ophthal. (1976) 60, 794

Radiation treatment of cancer of the eyelids

M. LEDERMAN
From the Royal Marsden Hospital and Moorfields Eye Hospital, London

Eyelid cancers are not uncommon tumours and are usually basal cell or more rarely squamous cell in character. Their importance lies in their special situation since unlike cancer arising elsewhere in the skin they can by their natural progression or as a consequence of the effects of treatment cause impairment or even loss of vision. Although these tumours are 'malignant', death of the patient rarely results from failure of local control, unless the disease is very advanced or was mismanaged at the outset. In the case of squamous cell cancer, death may occasionally result from metastatic spread.

It should be an obvious ethical maxim that no patient should be submitted to a major surgical operation if an established and equally effective alternative non-surgical procedure is available. In the case of skin cancer generally and the lids in particular radiotherapy provides such an alternative since its curative value has been firmly established during the past 50 years. The reluctance of ophthalmologists to advise the use of radiant energy appears to relate to the calamities that first attended its use by the pioneer ophthalmologists at the beginning of this century. The story of their heritage of ocular disasters has been transmitted from generation to generation ignoring the fact that progress in radiotherapy has been such that under modern conditions most of the complications, particularly the more gruesomely destructive ones, can largely be avoided. In view of this the present-day tendency to submit patients suffering from lid neoplasms indiscriminately to simple excisional or plastic surgical procedures without considering an established alternative would seem unjustifiable.

This report on a series of 896 patients (Table I) seen at the Royal Marsden Hospital during the period 1945–70 describes some of the features of the natural history of lid cancer and by giving the results, contraindications, and complications of radiation treatment evaluates this method in the treatment of lid cancer. The series is a relatively large one and the high proportion of 'previously untreated' cases reflects the value of the long-standing liaison the Royal Marsden Hospital has had with the main eye hospitals in London and also it is to be hoped demonstrates the confidence that many ophthalmologists have in radiotherapy.

Histological verification was obtained in 562 of the 630 cases of basal cell carcinoma. In most of the 68 cases lacking verification, a biopsy was taken but this proved inadequate or was otherwise unsatisfactory and by the time the report became available the treatment had reached a stage where repetition of the biopsy would have provided no useful information.

There is some doubt concerning the diagnosis of one case of squamous carcinoma. The inclusion of the 10 per cent of patients who lack histological confirmation can be excused because the clinical diagnosis of a basal cell carcinoma of the skin is usually easy and the response to radiation typical. In any event this proportion of the cases is small enough not to vitiate the conclusions drawn from this study.

Of the 689 previously untreated patients a number had had an excision biopsy before radiotherapy: some 80 patients had had an attempted primary excision but were promptly referred for post-operative radiotherapy because the pathological report showed that removal had been incomplete.

The recurrent cases comprise those patients whose symptoms recurred after receiving some form of surgery or radiotherapy at other hospitals (104 excisions; three excision and radiotherapy; five radiotherapy; five excision and plastic repair). These patients were referred to the Royal Marsden Hospital for treatment after frank recurrence had taken place. The patients seen and not treated include those who were referred for an opinion, some who were advised to have surgery, and a few patients who refused treatment.

Table I *Squamous and basal cell carcinomas of eyelids and canthi*, 1945–70

Patients	*No.*
Previously untreated cases	689
Recurrent cases	117
Cases seen and not treated	90
Total	896

Address for reprints: M. Lederman, FRCR, Chairman, Division of Radiotherapy and Oncology, Royal Marsden Hospital, Fulham Road, London SW3 6JJ

Tables II*a*, *b* show the regional distribution of the tumours in relation to their sex incidence. The well-known preponderance of tumours on the lower lid and inner canthus is well shown. The basal cell carcinomas are approximately 10 times more common than the squamous carcinomas but the latter form a higher proportion of the tumours of the upper lid and outer canthus. The sex ratios are male/female: 1·23 for the basal cell carcinomas and 2·93 for the squamous carcinomas.

Table III shows the age incidence illustrating the fact that most of the patients are elderly.

Table IV shows there is little of significance in relation to site or sex: but in the basal cell carcinomas there would appear to be a right-sided male predominance while in females the inner canthus lesion was more common on the left side.

Topographical distribution

It is customary to divide the site of origin of lid tumours into upper and lower lid; inner and outer canthus. However, in most early lid tumours it is possible to be more precise with regard to the particular part of the lid from which the tumour arises. In Fig. 1 the palpebral structures have been divided into their anatomical components—that is, inner and outer canthus and ciliary, tarsal, and palpebral parts for each lid. It has proved possible to allocate some 80 per cent of tumours of the upper lid and 90 per cent of those of the lower lid to one of these three sites of origin. For the more extensive tumours where the lid is involved for its whole extent the term 'whole' has been used and for the very advanced cases with involvement of the globe or orbit the term 'unclassifiable' has been employed.

Table IIa *Basal cell carcinoma. Distribution according to site and sex (630 patients)*

	Male		*Female*		*Total*	
Site	*No.*	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*
Upper lid	45	12·9	29	10·3	74	11·7
Lower lid	215	61·8	171	60·6	386	61·3
Inner canthus	76	21·8	77	27·3	153	24·3
Outer canthus	12	3·5	5	1·8	17	2·7
Total	348	100	282	100	630	100

Table IIb *Squamous carcinoma. Distribution according to site and sex (59 patients)*

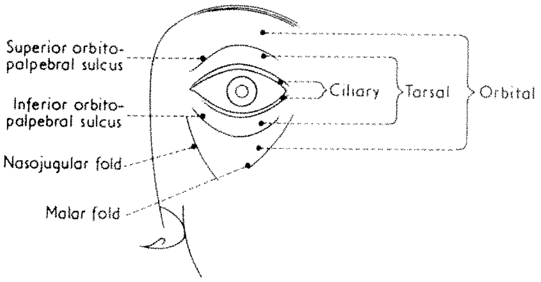
	Male		*Female*		*Total*	
Site	*No.*	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*
Upper lid	16	36·4	3	20·0	19	32·2
Lower lid	17	38·6	8	53·3	25	42·3
Inner canthus	5	11·4	4	26·7	9	15·3
Outer canthus	6	13·6	—	—	6	10·2
Total	44	100	15	100	59	100

Table III *Carcinomas of eyelids and canthi. Age incidence of new cases*

	Basal cell		*Squamous cell*	
	Male	*Female*	*Male*	*Female*
Average ages (years)	60·8	64·2	61·0	65·5
Youngest	20	18	34	49
Oldest	87	94	87	88

Table IV *Laterality by site and sex*

Basal cell carcinoma	*Males*		*Females*	
Site	*Left*	*Right*	*Left*	*Right*
Upper lid	16	29	11	18
Lower lid	98	117	85	85
Inner canthus	36	40	48	29
Outer canthus	6	6	3	2
Total	156	192	147	134
Squamous cell carcinoma				
Upper lid	8	8	1	2
Lower lid	9	8	4	4
Inner canthus	4	1	4	—
Outer canthus	1	5	—	—
Total	22	22	9	6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Inferior orbito-palpebral sulcus
Nasojugular fold
Malar fold
Ciliary
Tarsal
Orbital

FIG. 1 *Anatomical subdivisions of the lid*

Table V shows the topographical distribution according to the scheme outlined above. It can be seen that in both upper and lower lids the tarsal portion is most commonly affected but the ciliary portion is affected three times as frequently in the lower lid than the upper; whereas in the upper lid the orbital portion is affected nearly three times as commonly as in the lower lid.

The incidence of advanced tumours is also very

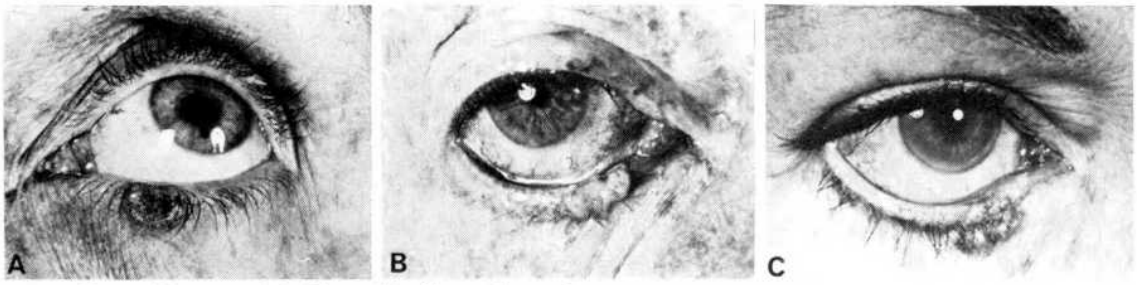

FIG. 2 *Lower lid tumours.* (a) *ciliary*; (b) *ciliary*; (c) *tarsal*

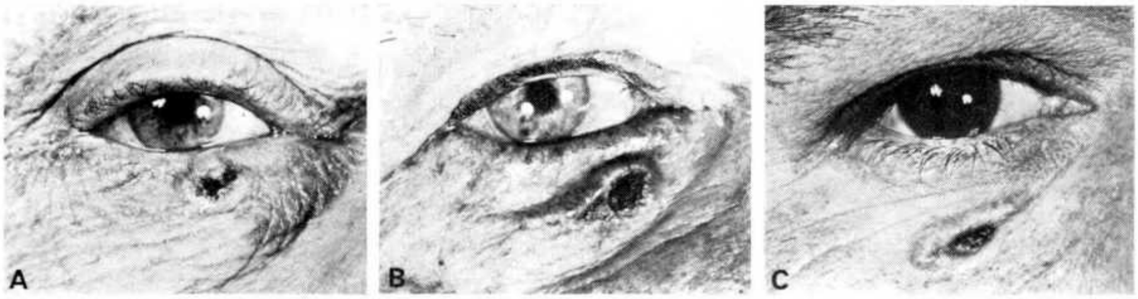

FIG. 3 *Lower lid tumours.* (a) *tarsal*; (b) *tarsal*; (c) *orbital*

Table V *Topographical subdivision (689 patients)*

Site	*Basal cell*		*Squamous cell*		*Total*	
Upper lid	*No.*	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*
Ciliary	12	16	1	5	13	14
Tarsal	32	43	5	25	37	40
Orbital	21	28	5	25	26	27
Whole	6	8	7	36	13	14
Unclassifiable	3	4	1	5	4	5
Total	74	80	19	20	93	100
Lower lid						
Ciliary	116	30	8	32	124	30
Tarsal	189	48	15	60	204	50
Orbital	43	11	1	4	44	10
Whole	30	7	1	4	31	7
Unclassifiable	8	2	—	—	8	2
Total	386	94	25	6	411	100
Inner canthus	53	95	9	5	162	100
Outer canthus	17	73	6	27	23	100
Total	630		59		689	

different in each lid. Nineteen per cent of the upper lid tumours are advanced (whole and unclassifiable) as opposed to 9 per cent in the lower lid. The reasons for this are possibly:

1. The greater incidence of ciliary lesions on the lower lid which are more likely to produce irritative symptoms.
2. The presence of epiphora if the lower punctum is involved.
3. On gazing directly at the eye the whole of the lower lid is open to inspection by the patient whereas to see the whole of the upper lid the affected eye has to be closed or the lid pulled down and inspection is therefore much more difficult.

Figs 2 to 6 illustrate the different topographical sites. The differentiation between ciliary and tarsal lesions is often difficult but in Fig. 2 it can be seen that in early lesions the lashes provide a reasonable baseline for identification. In the ciliary site the tumour is above the lashes or the lashes bisect it equally, whereas in the tarsal lesion the lash margin may be free or if it is involved the bulk of the tumour is below this line. The separation between tarsal and orbital lesions rarely presents problems although when both parts of the lid are affected the bulk of the tumour is usually on one or other side of the orbitopalpebral sulcus. Loss of lashes in relation to the tumour may occur with both tarsal and ciliary lesions, but usually the remaining lashes help in identifying the level of origin of a given tumour.

Figs 7*a*, *b* (Mustardé and Jones, 1970) show schematically the direction and site of insertion of the main fasciculi of the orbicularis oculi muscle.

It is not too difficult to imagine the similarity between the distribution of these sphincteric fasciculi and the sites of origin of the overlying skin tumours. Equally the frequency with which the inner canthus and lower lid are involved seems to be reflected in the manner and site of insertion of the muscle fibres.

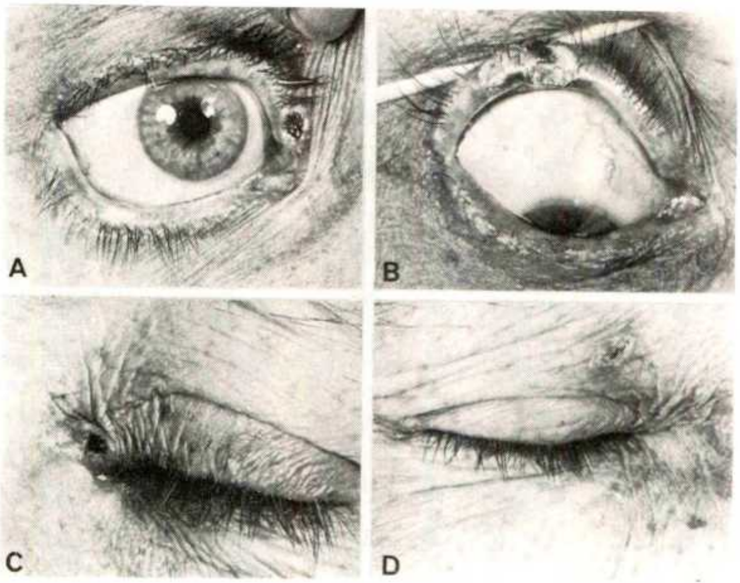

FIG. 4 *Upper lid tumours.* (a) *ciliary;* (b) *ciliary;* (c) *tarsal;* (d) *orbital*

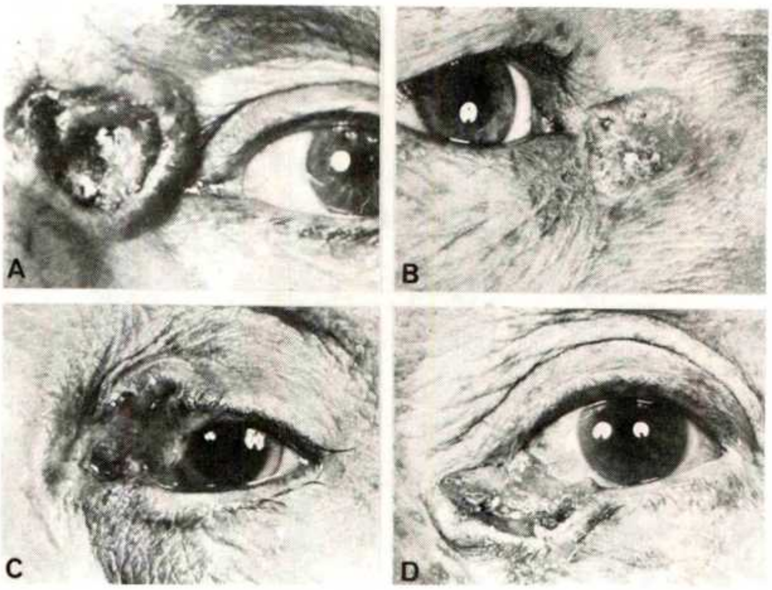

FIG. 5 *Inner canthus.* (a) *commissure free;* (b) *invasion of commissure;* (c) *invasion of upper lid;* (d) *invasion of lower lid*

That this should be so is within the bounds of legitimate speculation since in other parts of the body cancer tends to arise in relationship to sphincteric mechanisms (Lederman, 1964). This is particularly so in the case of the upper air and food passages where the direction taken by food and air on entering the body is controlled by a series of strategically situated complex sphincters. Cancer does not occur haphazardly in the upper air and food passages but mainly at those sites of physiological activity corresponding to the sphincteric regions. It is suggested that a comparable relationship exists between the orbicularis oculi sphincter and the epithelial tumours arising from its integumentary covering.

The occurrence of multiple lesions on the lid which may be either synchronous or consecutive is another feature characterizing sphincteric cancers. The multiple lesions illustrate the tendency that exists towards 'cancerization' of the whole of a

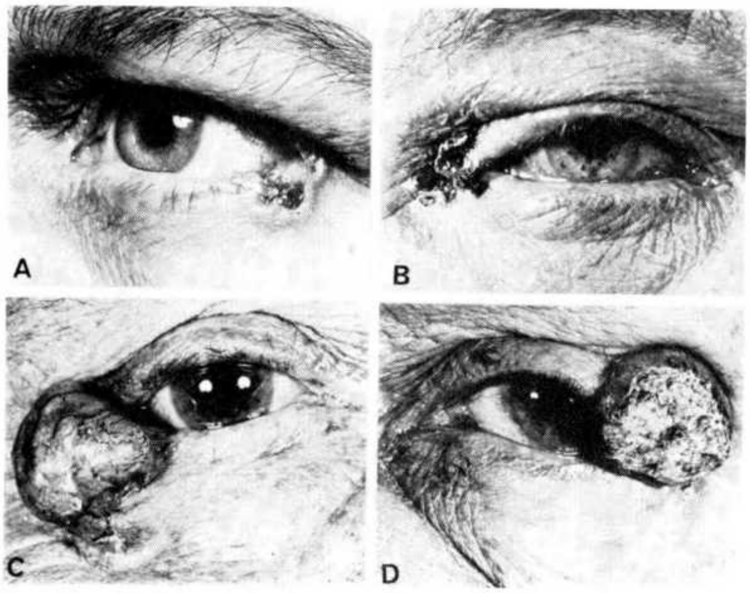

FIG. 6 *Outer canthus.* (a) *invasion of lower lid;* (b) *invasion of upper lid;* (c) *invasion of canthus and lower lid extending down to the orbital part of the lid;* (d) *invasion of canthus with extension into the tarsal and orbital part of the upper lid*

given sphincteric mechanism. In this series there were 19 patients with basal cell carcinoma who presented with multiple lid tumours. Thirty-three patients had multiple tumours involving lids and other parts of the skin, and 24 subsequently developed further skin tumours not necessarily of the lid.

Among the squamous cancers three patients had multiple lid tumours, four had multiple skin cancers, and three later developed other skin tumours.

TNM classification (UICC, 1974)

There is a special committee of the International Union against Cancer (UICC) (designated the Committee on Clinical Stage Classification and Applied Statistics) one of whose functions it is to extend the general technique of classification to cancer at all sites.

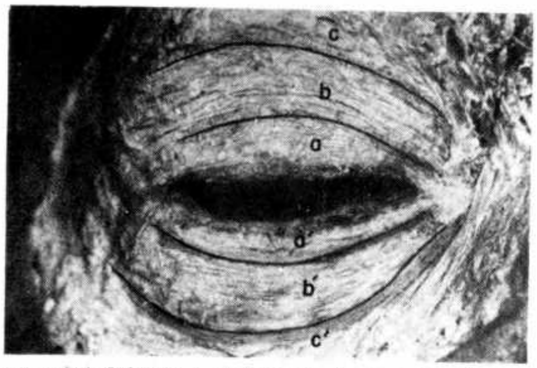

FIG. 7(*a*) *Orbicularis oculi muscle.* (a-a′) *pretarsal part;* (b-b′) *preseptal part;* (c-c′) *orbital part*

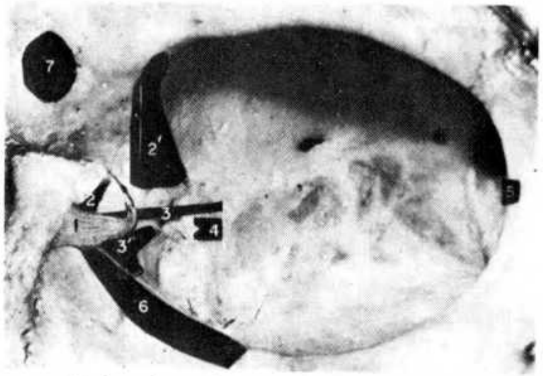

FIG. 7(*b*) *Insertions of the orbicularis oculi muscle.* (1) *medial canthal tendon made up of superficial heads of pretarsal muscles;* (2-2′) *Superciliaris and upper orbital muscle;* (3-3′) *preseptal muscles;* (4) *deep heads of pretarsals;* (5) *lateral canthal tendon of pretarsal muscles;* (6) *lower orbital muscle* (*from* Ophthalmic Plastic Surgery Up-to-Date, *Lester T. Jones*)

Tumour classification is important and where adopted internationally has the following advantages:

1. It provides a means of communication that transcends language barriers.
2. It assists in the evaluation and comparison of treatment results.
3. It helps in the selection of treatment methods.
4. It aids prognosis.

Many cancer sites have been the subject of study by this Committee and international agreement has been reached on some.

A classification for skin cancer has been recommended by the Committee and is meant to be applicable to tumours of the eyelids. In practice its implementation is difficult since it is dependent on tumour measurements and the dimensions it selects (2 and 5 cm) as a basis for classification are not readily relevant to the average lid tumour, Table VI.

In this series of cases the precise dimensions of the tumour were not routinely recorded since the site and extent of the lid involvement was expressed in topographical terms so as to indicate the manner and direction of tumour spread. However, some idea of the size of the tumour can be obtained from the maximum dimension of the field size used in treatment (this usually included a minimum margin of 5 mm of apparently normal skin surrounding the lesion) (Halman and Britten, 1960). Tables VII*a, b* show the distribution of the basal cell and squamous cell carcinomata according to the field sizes used in treatment. The tumour of 3 cm or less would presumably correspond to the T1 group, the 3 to 3·9 group to T2, and greater than 4 cm to T3 and T4. There were only three N1 cases in the squamous group.

Table VI *TNM classification applicable to tumours of the skin of the eyelid (UICC, 1974)*

T—*Primary tumour*

TIS	Pre-invasive carcinoma (carcinoma *in situ*).
T0	No primary tumour present.
T1	Tumour 2 cm or less in its largest dimension, strictly superficial or exophytic.
T2	Tumour more than 2 cm but not more than 5 cm in its largest dimension *or* with minimal infiltration of the dermis, irrespective of size.
T3	Tumour more than 5 cm in its largest dimension *or* with deep infiltration of the dermis, irrespective of size.
T4	Tumour involving other structures such as cartilage, muscle, or bone.

N—*Regional lymph nodes*

The clinician may record whether palpable nodes are considered to contain growth or not.

N0	No palpable nodes.
N1	Movable homolateral nodes. N1*a* Nodes not considered to contain growth. N1*b* Nodes considered to contain growth.
N2	Movable contralateral or bilateral nodes. N2*a* Nodes not considered to contain growth. N2*b* Nodes considered to contain growth.
N3	Fixed nodes.

M—*Distant metastases*

M0	No evidence of distant matastases.
M1	Distant metastases present including lymph nodes beyond the region in which the primary tumour is situated *or* satellite nodules more than 5 cm from the border of the primary tumour.

Table VIIa *Basal cell carcinoma: new cases*

Site	*Field size*			
	<3 *cm*	3–3·9 *cm*	≥ 4 *cm*	*Total size unknown*
Upper lid (no.)	28	32	13	73
Percentage	38·4	43·8	17·8	100·0
Lower lid (no.)	139	166	79	384
Percentage	36·2	43·2	20·6	100·0
Inner canthus (no.)	96	40	16	152
Percentage	63·2	26·3	10·5	100·0
Outer canthus (no.)	5	8	4	17
Percentage	29·4	47·1	23·5	100·0
Total (no.)	268	246	112	626
Percentage	42·8	39·2	18·0	100·0

Note: 4 cases with unrecorded field size excluded

Table VIIb *Squamous cell carcinoma: new cases*

Site	*Field size*			
	<3 *cm*	3–3·9 *cm*	≥ 4 *cm*	*Total size unknown*
Upper lid	7	2	10	19
Lower lid	10	15	—	25
Inner canthus	3	4	2	9
Outer canthus	—	2	3	5
Total (no.)	20	23	15	58
Percentage	34·5	39·6	25·9	100·0

Not: 1 case with unrecorded field size excluded

Results of treatment

In assessing the results obtained in the treatment of basal cell carcinomas the five-year survival rate customarily adopted as a measure of success for cancer generally is applicable with certain reservations since in the head and neck basal cell carcinomata do not metastasize and even if untreated the patient may survive many years. A simpler and more acceptable parameter for assessing the success or failure of treatment is to base this on the recurrence-free rate. Tables VIII*a, b* show this for basal cell carcinoma of the different sites. Only two patients actually died of uncontrolled disease, although in three other cases the cause of death was unknown.

A recurrence-free rate of at least 90 per cent or

Table VIIIa *Basal cell carcinoma. Recurrence-free rates (all sites and all patients)*

Lower lid (all sites)		*Inner canthus*	
Initially at risk = 386		Initially at risk = 153	
Recurrence-free		*Recurrence-free*	
Years	*Percentage*	*Years*	*Percentage*
1	97·3	1	94·7
2	95·9	2	93·2
3	95·3	3	91·7
4	95·0	4	90·8
5	94·3		
10	93·7		
>10	None	>4	None

Table VIIIb *Basal cell carcinoma*

All patients: upper lid (all sites)

74 initially at risk
No recurrences in a maximum period of observation of 15 years

All patients: outer canthus

17 initially at risk
1 recurrence only—within 1 year

more establishes the value of radiation treatment since unless the sample is small or case selection, or more commonly, dubious statistical manipulation has taken place, there is no cancer site in the body however early the lesion where a 100 per cent cure rate is achieved.

In the case of the squamous carcinomas with their potentialities for metastasis a different mode of presentation of results is necessary. To emphasize the greater gravity of these lesions even when affecting the skin, the recurrence-free rate, the crude survival rates, and the incidence of lymph node metastases are given in Tables IX and X. One-third of the patients died within five years but of these only three succumbed to their cancer and in four cases the cause of death was unknown: the remaining deaths were due to intercurrent disease.

Complications

In the 22 years between the publication of *Textbook of Ophthalmology*, vol. V (Duke-Elder, 1952) and *System of Ophthalmology*, vol. XIII (Duke-Elder, 1974) Duke-Elder's views on the relative roles of radiotherapy and surgery in the treatment of eyelid tumours underwent a profound change. In 1952 Duke-Elder stated that 'excision should be the rule and radiation the exception' whereas in 1974 he considered that 'excision or radiotherapy . . . are probably equally effective . . . when efficiently carried out'.

In common with Haye, Jammet, and Dollfus (1965) Duke-Elder emphasizes that the fear of radiation complications is often the main reason for preferring surgery to radiotherapy. There is little doubt that were it possible to establish that lid tumours could be treated by radiotherapy with an acceptable minimum of complications a formidable case could then be made for its preferential use.

Table XI lists the complications encountered in this series of cases. Three complications are not specially listed:

Telangiectasia with or without depigmentation (12 per cent)

The radiotherapist's attitude towards telangiectasia should parallel that taken by the surgeon towards postoperative scars. There is no guarantee that any scar whether surgical or radiational will always be cosmetically acceptable although much can be done technically by both the surgeon and the radiotherapist towards achieving a satisfactory non-disfiguring scar.

Table IX *Squamous cell carcinoma. Survival rate by site*

Site	*Patients at risk 5 years and followed-up*	*Alive 5 years*	*5-year survival (percentage)*
Upper lid	18	12	67
Lower lid	23	18	78
Inner canthus	6	2	—
Outer canthus	4	2	—
Total	51	34	67

Table X *Recurrence-free rate for all sites. Lymph node involvements (59 patients)*

Site	*Not involved*	*Involved*		*Total*
		Initially	*Later*	
Upper lid	16	2	1	19
Lower lid	25	—	—	25
Inner canthus	8	—	1	9
Outer canthus	4	2	—	6
Total	53	4	2	59

In nine previously treated cases, two had nodes involved later
Recurrence-free percentage: 1 year (87·5 per cent)
No recurrences observed beyond 1 year

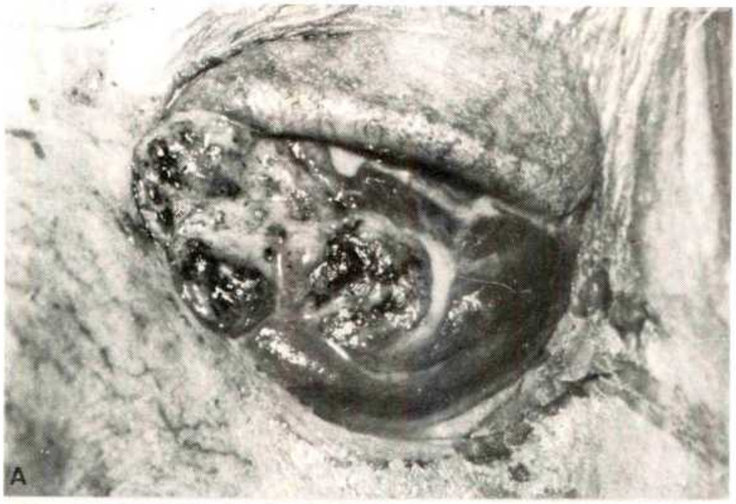

FIG. 8(*a*) *Extensive carcinoma of lower lid before treatment*

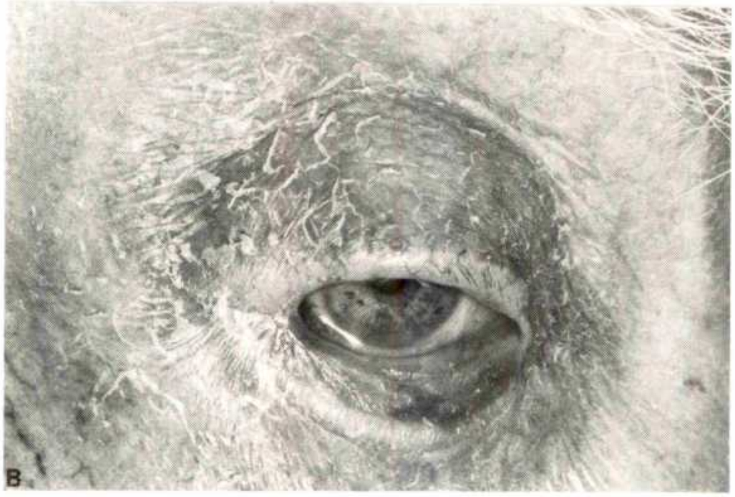

FIG. 8(*b*) *After treatment showing lid deformity*

Lid deformity (7 per cent)

As many of the patients are elderly they have a natural tendency to laxness of the lower lid or even ectropion. If already existing this can be aggravated by radiotherapy. Alternatively, when a lid has been infiltrated by neoplasm for its whole thickness healing after radiation will be accompanied by fibrosis and when the tarsal plate is affected a contraction deformity will ensue. This type of deformity, usually ectropion, almost exclusively affects the lower lid. In the case of the upper lid, infiltration and destruction of the tarsal plate tend after successful radiation treatment to result in a coloboma rather than in a cicatricial deformity, Figs 8, 9, 10*a*, *b*.

Epiphora (10 per cent)

The possible occurrence of postradiation epiphora is frequently advanced as an argument against the use of radiotherapy. However, the obliteration or loss of the upper punctum occasions no problem: only when the lower punctum and canaliculus are stenosed or destroyed may epiphora occur. Mustardé and Jones (1970) in discussing the reconstructive surgery of the medial canthus point out that it is possible to remove the lacrimal passages completely without epiphora. After such an event epiphora will occur only in the presence of conditions giving rise to excessive tear formation. These are listed as being high wind, undue exposure of the conjunctiva, and in particular ectropion and also inflammatory conditions involving the lid margin, conjunctiva, cornea, or lacrimal sac.

These observations are supported by the events after radiation obliteration of the lacrimal passages. Only a small proportion of the patients in this

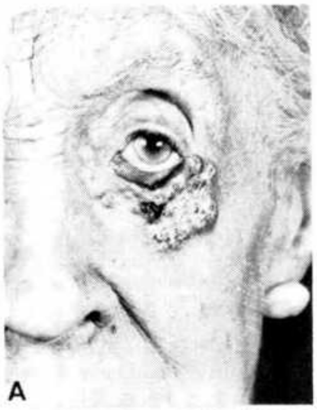

FIG. 9(*a*) *Extensive tumour of left lower lid with invasion of fornix and destruction of tarsal plate*

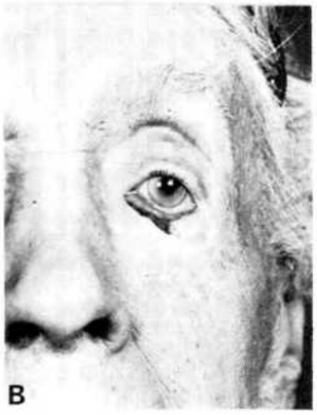

FIG. 9(*b*) *After treatment*

series (10 per cent) developed a troublesome epiphora and these were usually patients with a degree of lid deformity or some other local cause of reflex increase of tears.

This ability of the eye to accommodate itself to loss of the lacrimal passages means that attempts to maintain the patency of the punctum during or after radiotherapy, by irrigation, intermittent dilatation, the insertion of various kinds of dilator or operation are unnecessary. Efforts should rather be directed to ensuring that every cause of irritation that might give rise to a reflex increase in tear production should be sought and eliminated.

There is one factor that operates to the advantage of the patient with postradiation as opposed to postsurgical epiphora and that is that in many cases the epiphora appears to be self-limiting, tending to subside spontaneously within a year of treatment. The reason for this fortunate event is that radiation not only produces stenosis of the punctum but also destroys some of the secretory glands of the lid and conjunctiva so that there is a reduction in the total quantity of tears produced. At some point the impaired secretory mechanism and the damaged drainage system enter into compensatory equilibrium and the patient's eye no longer weeps.

OTHER COMPLICATIONS, Table XI

Keratinization of the conjunctival mucosa occurred in 5·6 per cent of cases. When this affected the lower lid problems could be avoided by regular removal of the keratin plaque and most patients can be taught to do this themselves. In the upper lid the keratin plaque is a potential menace to the cornea and a contact lens may be required to avoid corneal damage. Fortunately in recent years keratinization is less likely because of modifications in radiation technique whereby intense reactions are avoided.

Lid necrosis has occurred in patients with moderately atrophic skin changes or those with surgical scars. As a rule these necroses seem to occur in summer after exposure to an intense and unaccustomed degree of sunlight. The avoidance of bad scars, warning the patients against direct

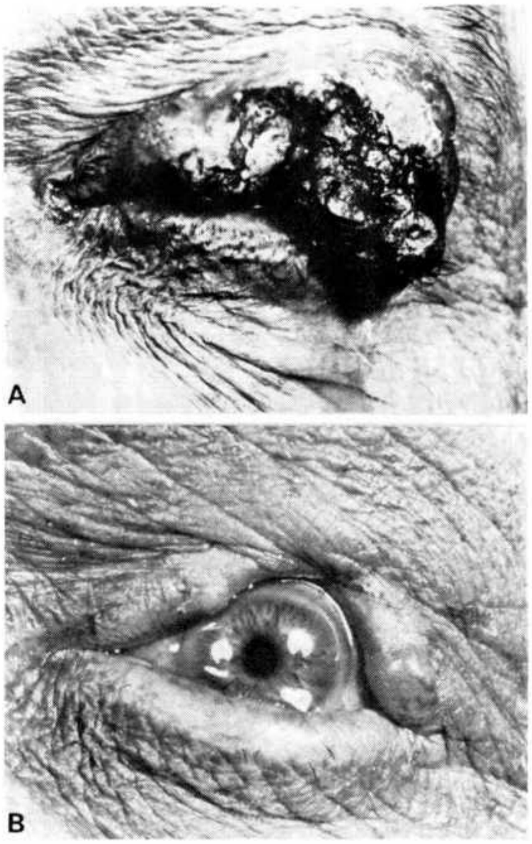

FIG. 10 (a) *Extensive tumour of upper lid with destruction of part of the tarsal plate;* (b) *after treatment showing lid coloboma*

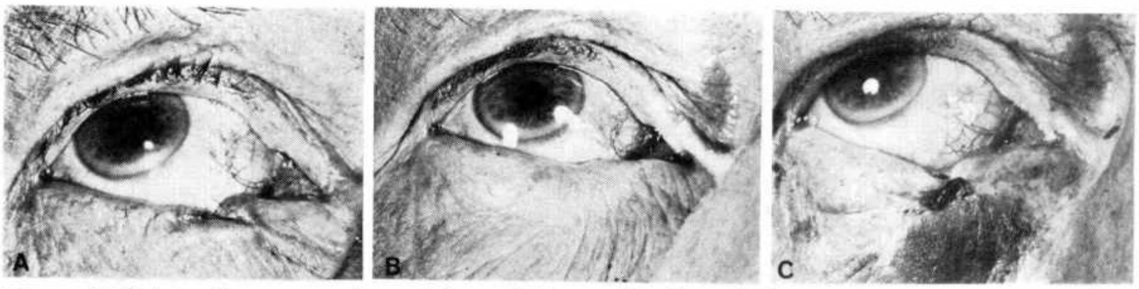

FIG. 11 (a) *Postoperative recurrence in scar before radiotherapy*; (b) *after radiotherapy*; (c) *skin necrosis after exposure to excessive sunlight*

Table XI *Incidence of complications*

Complication	*Basal cell*		*Squamous cell*	
	No.	*Percentage*	*No.*	*Percentage*
Lid necrosis	18	2·9	4	
Keratinization	35	5·6	3	
Corneal ulceration or opacity	10	1·6	1	
Corneal abrasion or keratitis	13	2·1	1	
Cataract	5	0·8	—	
Eye removed	3	0·5	1	
Any complication	84	13·3	10	16
Total	630		59	

exposure of the lids to intense sunlight, and the use of barrier creams all help. These sunlight-induced necroses heal readily with the application of a corticosteroid ointment once the solar-exposure factor is removed.

The corneal complications encountered were not due to direct irradiation of the cornea since in nearly all cases complete shielding of the cornea was achieved. Most of the corneal complications were due to exposure or irritation from secondary changes in the lid. The radiation cataracts occurred in patients treated by gamma radiation, usually in the form of a radon seed implant. In no case was it found necessary to deal with the cataract surgically. Of the three cases where the eye was lost, in two the eye was removed before the patient was referred for radiotherapy and in the third case a useless eye was removed because of involvement by uncontrolled disease.

Prevention of complications

GENERAL MEASURES

Patients undergoing the irradiation of a lid tumour inevitably develop a radiation reaction in the treated area. While this lid reaction ultimately subsides and is generally followed by few complications, the related bulbar conjunctiva and the cornea may, as already noted, be secondarily affected even though total protection of these tissues against irradiation has been provided. In addition many of the patients in the age groups concerned have incidental ocular problems requiring skilled care while the patient is undergoing radiotherapy. Because of this there is imperative need for ophthalmological control and care of the patient during treatment and the ophthalmologist has a vital part to play in any radiation unit dealing with these cases if unnecessary complications are to be avoided.

CONTRAINDICATIONS TO RADIOTHERAPY

The misuse of radiotherapy is understandable since it is a non-operative procedure readily available and easily applied. However, if complications are to be eliminated or reduced in frequency then the radiotherapist must be on his guard not to be enticed into treating a patient in circumstances where complications are inevitable or when treatment is accompanied by a high risk of postradiation damage. In these circumstances it is clearly better for the patient to submit to alternative, non-radiational methods. If no alternative is available or if available would entail removal of the eye then the radiation risks may be accepted as the lesser of two evils but this should be done only after a full discussion with both the patient and his doctors.

The following may be accepted as contra-indications to radiotherapy:

Recurrence after previous treatment

Recurrent cases, whether the previous treatment be surgical or radiotherapeutic, should in principle be surgically treated if possible. If surgery is impractical then radiotherapy can be used, again with a good prospect of controlling the neoplasm but at an increased risk of a cosmetically unwelcome cicatrix and an added risk of radionecrosis. In this series of cases 3·8 per cent of the previously untreated patients were referred for surgery after radiotherapy either because of incomplete tumour regression or frank recurrence.

Disease involving the mid-third of the upper lid

Lesions in this situation are readily curable by radiotherapy but in the event of undesirable mucosal changes such as keratinization, secondary damage to the cornea is highly probable. This restriction on the use of radiotherapy in upper lid tumours applies only to small tumours centrally situated which would be amenable to simple excision and closure by direct approximation. If an upper lid tumour is sufficiently extensive to require a complicated reconstruction radiotherapy becomes a desirable alternative, since not only are the results excellent but there is always a good chance that keratinization may be avoided and even if it does occur and proves troublesome a contact lens provides a remedy. A sense of proportion has to be preserved in connexion with the risks of keratinization and no patient, particularly if elderly, should be persuaded to undergo a complicated and serious operation on the physiologically important upper lid unless some overriding reason other than the possibility of postradiation mucosal keratinization exists.

The presence of a damaged cornea

When the lid tumour is related to a cornea that is already abnormal or damaged in some way then as any subsequent postradiation lid changes may add further injury to the already damaged cornea surgery should be considered.

Skin changes

In outdoor workers or light-skinned patients, who already have solar skin changes, irradiation should be avoided especially if the patient lives in a tropical or subtropical climate.

Bone invasion

Radiotherapy is rarely successful in eradicating a tumour which has invaded bone. The advanced rodent ulcer accompanied by orbital bone invasion is best treated by a preliminary course of radiation followed by radical surgery.

A very small lesion remote from the canthus and lid margins

Radiotherapy should be avoided in cases in which a biopsy excision would adequately remove the tumour.

TECHNICAL MEASURES

The technical steps the radiotherapist can take towards reducing the complications affecting the lids, conjunctiva, and the eye relate to the selection of apparatus and the dose and time factors of the treatment. Unwelcome cosmetic sequelae are more likely where radiation energies of 60 kV or less are used and ocular complications are more likely when gamma-ray sources are implanted near the eye.

The intensity of the radiation reaction, the incidence of mucosal keratinization, and the cosmetic quality of the radiation scar can all be favourably influenced by attention to the fractionation of the dose and the length of the overall treatment time.

PROTECTIVE DEVICES (Lederman and Jones, 1966)

The normal eye and the unaffected parts of the lids should be completely shielded. It is important to avoid trauma and sepsis when inserting the protective lead eye shields or spatulae. Even when the lids, eye, and orbital contents are involved by disease it is still possible to protect the cornea and the intraocular structures deep to it. To do this the radiation field has to be delineated by a light beam and an indirect method of shielding is employed wherein a lead absorber is placed in the beam of radiation so that the part of the eye that has to be protected is brought within the shadow produced by the interposed absorbing material.

This indirect method of shielding is of great value not only in the presence of orbital invasion but whenever the lids or fornices are deformed or destroyed and the direct insertion of a lead protective device proves impossible or potentially traumatic to the eye.

ANCILLARY PROCEDURES

The use of a haptic contact lens as a means of protecting the cornea against damage from secondary changes in the lids has proved of great value. The two chief indications are:

1. When tumours of the upper lid require radiation treatment and the risks of keratinization have to be guarded against.
2. When both upper and lower lids, particularly the lid margins, require treatment.

The risk of undesirable postradiation changes in the lids with secondary damage to the cornea is directly proportional to the length of lid margin treated. In these two instances the contact lens is made and fitted before treatment and worn throughout treatment and the period of reaction. If the reaction settles down without any serious lid sequelae the lens can be abandoned: otherwise its permanent use may be necessary. In order to prevent exposure keratitis with secondary keratinization or opacification of the cornea the patient with a serious postradiation lower lid deformity should be considered for plastic surgical correction of the deformity before signs of corneal exposure become apparent.

Discussion

It is believed that the results obtained in this series of cases, even accepting the incidence and the nature of the complications, would justify and support the continued advocacy of radiotherapy as the treatment of choice for malignant lid tumours.

It is difficult to determine the part that surgery should play in the treatment of these tumours since a survey of the surgical literature, particularly publications emanating from plastic surgical sources, are devoted almost exclusively to detailed accounts of surgical techniques. Any prolonged acquaintance with the treatment of malignant disease will demonstrate that cancer is no respecter of surgical expertise and for any given surgical procedure for lid cancer to be acceptable careful objective evaluation is necessary. If the rigid standards adopted by radiotherapists are to be followed it is essential that the description of any given operation be accompanied by its contraindications, complications, and the success rate achieved over at least a five-year period of observation. Nevertheless it must be accepted that in spite of the reliable results and obvious advantages of radiotherapy some cases are better treated by surgery particularly those contraindicating radiotherapy.

Any further scope for surgery should, assuming the patient is fit for operation, depend on the tumour size and situation and hence the simplicity or complexity of the operation needed.

If the size of tumour in this series (Tables VII*a*, *b*) is taken as representative it will be seen that of the basal cell carcinomas approximately one-third of the lid tumours and two-thirds of the inner canthus tumours would fall into category T1 of the UICC system of classification. This means that allowing for a 5 mm margin of normal tissue these tumours were 2 cm or less in diameter and therefore presumably suitable for an operation not requiring plastic lid reconstruction (Mustardé and Jones, 1970). It should be noted that it is precisely these early cases that give the best results and fewest complications with radiation treatment. However, the remaining patients, namely the majority, would require excision and lid reconstruction with all that that entails by way of availability of the requisite surgical skills, the surgical risks for the elderly patient, to which must be added the economic disadvantages of surgical as opposed to radiotherapeutic treatment.

As neither surgery nor radiotherapy is a specific remedy for cancer, debate on their respective merits can prove endless. Effort can most profitably be expended on determining their relative spheres of usefulness in a complementary rather than a competitive sense. Until such time as more evidence concerning the true scope and value of surgery, particularly when associated with plastic lid reconstruction becomes available the patient's interests can best be safeguarded by ensuring collaboration between surgeon, radiotherapist, and dermatologist so that therapeutic decisions based on a partisan approach are avoided if possible.

I thank the many ophthalmologists who by sending their cases have made this study possible. I wish to single out in particular the members of the staff of the Moorfields Eye Hospital, City Road and High Holborn, and the Royal Eye Hospital. I am especially indebted to my colleagues at the Royal Marsden Hospital, Mr Shapland, Mr Wybar, and Mr Mallet, and to Mr Ruben of the High Holborn branch of Moorfields for dealing with the contact lens problems. I also thank Mr P. Payne, Director of the South Metropolitan Cancer Registry, for providing me with the statistical tables, and Miss Pegus and Mrs Potucek of the Medical Art and Photographic Departments of the Royal Marsden Hospital for the tables and illustrations. The editors of *Ophthalmic Plastic Surgery Up-to-Date* kindly gave permission to reproduce Figs 2 and 3 on page 4 of that book.

Dr B. Lewinsky, now at the Letterman Hospital, San Francisco, kindly helped with analysing the clinical material.

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Basal cell carcinoma in the eyelid region

J. R. O. COLLIN
From the South-East Thames Regional Plastic Surgery Unit, Queen Victoria Hospital, East Grinstead

The first recorded account of the surgical treatment of basal cell carcinoma is given by Jacques Daviel in an address to the Royal Society of London in 1755 (Bennett, 1974). He described four patients with ulcers in the 'great angle' of the eye and four patients with ulcers affecting the eyelids, all of whom he treated successfully with surgical excision. Stenbeck (1900) was the first to describe the cure of a basal cell carcinoma with irradiation and during this century much literature has been published showing increasingly successful results with both forms of treatment. Older, Quickert, and Beard (1975) finally approached the ultimate with a report of 157 cases of histologically proved eyelid basal cell carcinoma, none of which recurred during a follow-up period that varied between a few months and 18 years. The purpose of this paper is to assess a series of eyelid basal cell carcinomas which were operated on in a general plastic surgery unit and to draw attention to the risk involved if the primary treatment does not effect a complete cure.

Findings

INCIDENCE

Between 1965 and 1970, 261 patients had histologically proved basal cell carcinomas removed from the eyelid region at the South-East Thames Regional Plastic Surgery Unit. This represents an average of 43·5 patients a year. Payne (1966) assessed that the average incidence of carcinoma of the eyelids for this area of England was 6·5/100 000 males and 4·1/100 000 females. This means that this unit was surgically treating the expected incidence of eyelid tumours for a population of approximately one million people. However, there are obviously gross inaccuracies in the collection of skin cancer statistics in view of the numerous treatments available by different medical practitioners, and the lack of statutory necessity to report cases to the Cancer Registry.

Altogether 226 of these patients had notes available for follow-up study and they had 255 separate eyelid basal cell lesions. 10·6 per cent of patients, therefore, had more than one eyelid tumour and the percentage would have been higher if other regions had been included. These figures agree with those of Macomber, Wang, and Sullivan (1959) and Leventhal and Messer (1972). In this series three patients with multiple lesions had the naevoid basal cell carcinoma syndrome with dentigerous cysts.

SITE

The highest incidence was at the medial canthus and lower lid which agrees with Battle and Patterson (1960), Hayes (1962), and Payne (1966), but Holmström, Bartholdson, and Johanson (1975) and Older and others (1975) found there was a higher incidence on the lower lid than in the medial canthal area.

Site	*Percentage*
Upper lid	6·7
Lower lid	37·6
Medial canthus	38·4
Lateral canthus	7·1
Eyebrow	9·4
Orbit	0·8

SEX

60·2 per cent were males and 39·8 per cent females. This is supported by Payne (1966), Holmström and others (1975), and Brewitt, Hansen, and Huerkamp (1975), but Shulman (1962) and Older and others (1975) found that the sex incidence was about equal.

AGE

The peak incidence in this series was between 60 and 69 years (36·9 per cent of males and 31·3 per cent of females). This is in general agreement with Shulman (1962), Payne (1966), Fitzpatrick (1972), Rakofsky (1973), Meythaler (1973), Brewitt and others (1975), and Older and others (1975).

SIZE

Most of the lesions were between 5 mm and 2 cm in diameter, the highest incidence being between 1 and 2 cm. The average size of the lesions in the series of Fitzpatrick (1972) was 12 mm, but in the series of Holmström and others (1975) the average largest diameter was less than 10 mm. The recurrence rate was highest in cases of large tumours and this was confirmed

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by Battle and Patterson (1960), Von Essen (1960), Fitzpatrick (1972), and Older and others (1975).

Size of lesion	*Percentage*
Unspecified	10·2
'Small' or less than 5 mm	15·0
Between 5 and 10 mm	33·6
Between 1 and 2 cm	37·6
More than 2·5 cm to complete orbital involvement	3·6

TYPE OF SURGERY

All lesions were excised with a 3 to 5 mm macroscopic clearance of the lesion depending on the individual surgeon, and the defect was closed by:

Method	*Percentage*
Direct closure	29·8
Graft	9·8
Flap	60·4

All lesions were subjected to histological examination and if this showed an incomplete excision the patient was re-operated on. Such patients are not included in the figures given for recurrences.

HISTOLOGY

Most lesions were of the circumscribed common solid type and there was no very clearly defined pattern in the histology of those cases which recurred. However, 70 per cent of the lesions which did recur were described as morphoeic, invasive, or multicentric; 50 per cent of the recurrences occurred with medial canthal lesions. This is supported by Wiggs (1975).

FOLLOW-UP PERIOD

The aim with primary lesions in which histological examination had confirmed a complete excision, was to follow-up the patient for five years and in most cases this was achieved. Some patients, however, died, emigrated, failed to attend, or were followed-up by their own ophthalmologist, general practitioner, or dermatologist, and it is likely that many of these cases would have been referred back to this unit if they had developed a recurrence.

Time	*Percentage*
Less than 6 months	16·5
6 months to 1 year	6·3
1–3 years	21·3
3–6 years	45·2
7–11 years	10·7

Results

PRIMARY SURGERY

Altogether 176 patients presented for surgery having had no previous treatment. Four of these patients (2·3 per cent) had a recurrence and of these four, two of the histology reports showed complete clearance and the third did not specifically comment on the clearance. The recurrences in these three patients were all detected at routine follow-up and successfully excised. The fourth patient had a massive lesion involving both upper lids and extending across the bridge of the nose. He was referred for surgery from Ireland in view of the gross size of his carcinoma, and it seems surprising that he had not had any previous treatment but there was no record of this in his notes. He had an exenteration of one eye with removal of part of the malar bone, and excision of the medial third of the other upper eyelid. The histology report did not comment on clearance, presumably because much of the lesion had to be removed piecemeal. The carcinoma recurred four years later and an extensive resection of half of his face was undertaken, but clearance was incomplete and he died two years later.

PREVIOUS IRRADIATION

16·8 per cent or 38 patients out of the 226 in the series were referred for surgery with either a primary irradiation failure, a recurrence after irradiation, or an irradiation-induced lesion. 18·4 per cent (7/38) had a recurrence after surgery. Three of these seven patients had basal cell carcinomas which were reported as having been completely excised. The re-recurrence was detected at routine follow-up and successfully excised. Three other patients died of their basal cell carcinomas and the fourth is expected to die soon. This means that in this series if a lesion recurred after irradiation and was not cured at the first attempt with subsequent surgery, there was a 57·1 per cent chance of dying of the disease. It must however be conceded that of these four patients, two who died had gross lesions involving the whole orbit, the third had a 1·5 cm lesion in the medial canthal area and the fourth, who is expected to die shortly, had multiple multicentric basal cell carcinomas after nine courses of *x*-ray treatment of the face for acne in 1936. In all of these patients histological clearance of the lesion was suspect.

PREVIOUS SURGERY

Ten patients out of the 226 (4·4 per cent) presented for surgery between 1965 and 1970 with a recurrence after primary surgery. Three of these patients (30 per cent) had a re-recurrence and of these, two subsequently died of their basal cell carcinomas. One had had the lesion removed twice previously by ophthalmologists; on referral he had an exenteration and the specimen was reported as being morphoeic with complete clearance. The re-recurrence occurred five years later and with subsequent surgery it was not possible to obtain complete clearance. The other patient who died was only 24 years old when referred with multiple morphoeic basal cell carcinomas which had recurred after previous surgery. He had multiple operations and histologically the lesions were initially completely excised but recurrent lesions kept appearing. The third patient, who had a successful excision of the re-recurrence, was a known case of the naevoid basal cell carcinoma syndrome.

PREVIOUS COMBINED SURGERY AND IRRADIATION

Two patients came into this category, one of whom subsequently died of his disease. The first patient had had two previous courses of radiotherapy and one episode of surgery for an upper eyelid basal cell carcinoma. She had an enucleation on referral, histological examination showed complete clearance, and she has had no recurrence during a 5½-year follow-up. The second patient similarly had had two courses of radiotherapy and one episode of surgery for an inner canthal lesion. An extensive excision was carried out on referral which showed a morphoeic basal cell carcinoma apparently completely excised. The lesion recurred seven months later and was re-excised again with complete clearance histologically, but it again recurred six months later and this time was inoperable.

Discussion

A recurrence rate of 2·3 per cent during an average follow-up period of between three and six years for cases of basal cell carcinomas treated with primary surgery is in general agreement with the figures reported in other series: Rank and Wakefield (1958), 1·4 per cent; Hayes (1962), 3 per cent; Cobbett (1965), 3 per cent; and Binns and Sherriff (1975), 0·5 per cent. Older and others (1975), who reported a 100 per cent cure rate, attributed their success to the use of frozen section controls in 72 per cent of their cases. This certainly does seem to improve the chances of successful surgery but whether this is feasible for every patient in view of the good results anyhow obtainable with primary surgery, depends very much on the facilities available.

Beard (1975) has drawn attention to the unpredictable nature of basal cell carcinoma recurrence in relation to the histological clearance. In this series if a lesion was incompletely excised the patient was re-operated on, but in 8·4 per cent the histological examination showed a suspect clearance and in none did a recurrence develop. Conversely in 4·4 per cent of this series the histological examination showed complete clearance and there was a subsequent recurrence. Rakofsky (1973) operated on 95 patients in 47 of whom the histological study showed incomplete clearance. Of these 47, only 23·4 per cent actually developed a recurrence. Since we do not know which cases are going to recur we must aim at histologically-confirmed complete surgical excision. In this series it is unlikely that frozen section control would have improved the cure rate for cases treated with primary surgery in view of the fact that the recurrences in three cases occurred despite apparent complete clearance on routine histological examination.

Recently published recurrence rates of eyelid basal cell carcinoma treated with primary irradiation are of the same order as the recurrence rates after primary surgery: Fitzpatrick (1972), 4·8 per cent; Casanovas, Piñol, Oller, and Guix (1973), 2 per cent. The recurrence rate of 18·4 per cent for surgery to basal cell carcinomas which recur after irradiation is in general agreement with the recurrence rates reported by Rank and Wakefield (1958), 15·8 per cent; Hayes (1962), 24 per cent; Cobbett (1965), 20·5 per cent; and Sundell, Gylling, and Solvio (1966), 15·4 per cent.

The recurrence rate of 30 per cent for secondary surgery to lesions which have recurred after previous surgery is high, but 70 per cent of these patients in this series were referred from other areas of the country with extensive lesions. Von Essen (1960) reported a 22 per cent overall recurrence rate for previously treated skin carcinomas which were subsequently given radiotherapy, and this is of the same order of magnitude.

Conclusion

This series shows that the worst prognosis for basal cell carcinoma occurring in the eyelid region is carried by large lesions in the medial canthal area which have recurred after previous treatment with surgery or irradiation; histologically they are classified as morphoeic, multicentric, or invasive. 3·5 per cent of the patients in this series died of their disease. Eyelid basal cell carcinoma is therefore a potentially lethal condition and whatever form of treatment is undertaken should be meticulously performed because there is no doubt that the first treatment gives by far the best chance of success.

I wish to thank the surgeons of the Queen Victoria Hospital, East Grinstead, for permission to examine the notes of their patients and in particular Mr R. L. Beare for his help and encouragement. My thanks are also due to Mrs Becky Law for typing this paper.

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New vessel formation in retinal branch vein occlusion

JOHN S. SHILLING AND EVA M. KOHNER
From the Retinal Diagnostic Unit, Moorfields Eye Hospital, London

Neovascularization after retinal branch vein occlusion (RBVO) has long been recognized (Foster Moore, 1924; Jensen, 1936) and it has been noted more recently in a number of publications. Krill, Archer, and Newell (1971) found that three out of 14 patients had new vessel formation after RBVO; Michels and Gass (1974) found seven cases of retinal new vessels in 28 eyes and disc new vessels in two out of seven eyes.

We studied a series of patients with retinal branch vein occlusion. Our aim was to identify features in the clinical appearance and on fluorescein angiography that would indicate whether a patient with branch vein occlusion would develop new vessels and vitreous haemorrhage.

Patients and methods

PATIENTS

All patients with RBVO referred to the Retinal Diagnostic Department of Moorfields Eye Hospital during the last four years were assessed. Patients were included in the study if they presented within three months of their first visual symptom and had been followed-up for at least two years. Of the 87 eligible patients 19 were unable to attend the follow-up examination (two because they had died, the remaining 17 because they could not be traced or could not attend). This study therefore comprises 67 patients, who had 68 eyes affected by vein occlusion.

METHODS

All patients had ophthalmic and medical examinations. The eye assessment included a history of visual symptoms specifically related to vitreous haemorrhage; corrected visual acuity, direct and indirect ophthalmoscopy, and slit-lamp biomicroscopy. Colour photographs and fluorescein angiograms were performed at varying intervals, but each patient had at least three angiograms in the follow-up period of two years.

Colour photographs and fluorescein angiograms were examined for the site of vein occlusion, the presence of capillary dilatation (Fig. 1*a*), areas of capillary non-perfusion (Fig. 2), and the presence of neovascularization. The criterion for capillary non-perfusion was that an area of more than four disc diameters in size must be lacking capillaries on fluorescein angiograms. Cotton-wool spots are usually of a smaller diameter, although they are always associated with capillary non-perfusion. Areas covered by haemorrhage were not included, since haemoglobin absorbs fluorescence and could therefore give a false impression of capillary closure (Figs 1*b*, *c*).

Most patients with pronounced non-perfusion of capillaries (Fig. 2) had areas that were much larger than four disc diameters in size devoid of capillaries and in many these extended into the retinal periphery of which no photographs were available.

The following criteria were used to diagnose the new vessels:

1. The presence of abnormal vessels flat or in front of the retina or optic disc as seen by slit-lamp biomicroscopy, binocular indirect ophthalmoscopy, or stereoscopic photography (Figs 3*a*, *b*).
2. The fluorescein angiographic change of progressive leakage of dye from these vessels (Figs 3*c*, *d*).

Medical examinations were carried out on 50 patients within three months of their first visit to Moorfields Eye Hospital. The other 18 were examined at various times up to two years.

The examination was directed mainly towards the cardiovascular system. Investigations included: haemoglobin, packed cell volume, erythrocyte sedimentation

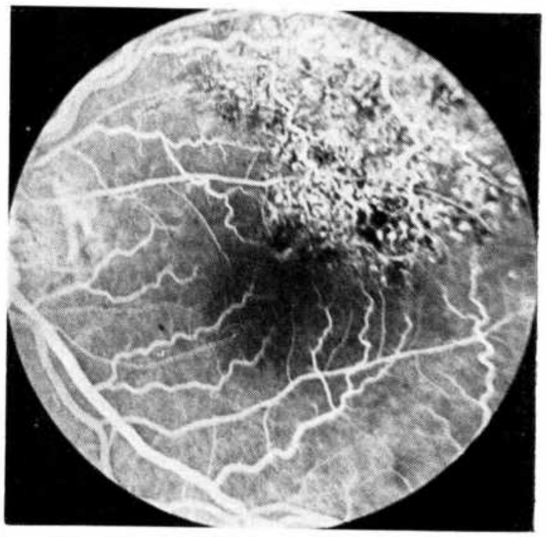


FIG. 1(a) *Fluorescein angiogram after absorption of haemorrhage, showing capillary dilatation*

Address for reprints: J. S. Shilling, FRCS, Eye Department, St Thomas's Hospital, London SE1 7EH rate, glucose tolerance test (in those under 65 years old), fasting serum cholesterol and triglycerides, plasma urea and uric acid estimation; measurement of serum proteins and electrophoresis. Serum electrolytes were estimated in hypertensive patients. All patients had an electrocardiogram and chest *x*-ray.

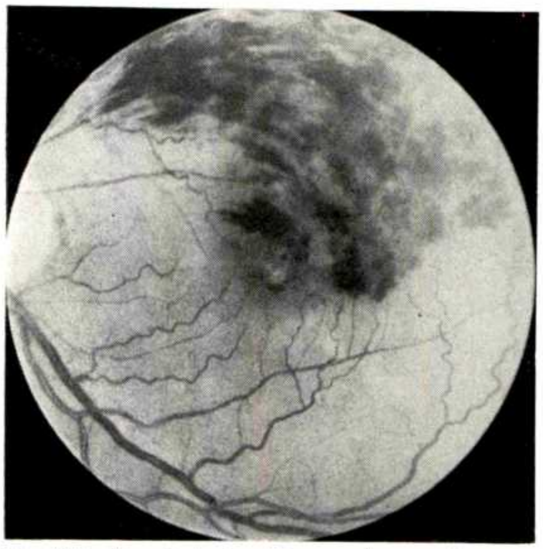


FIG. 1(b) *Same patient as Figs* 1a, c *from a colour photograph of a supero-temporal RBVO with retinal haemorrhages*

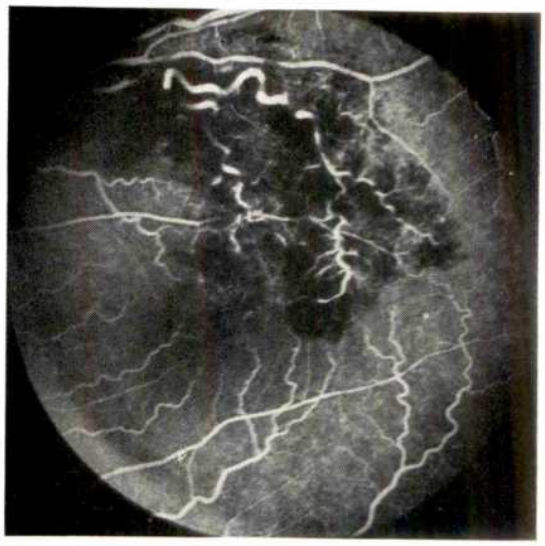


FIG. 1(c) *Fluorescein angiogram of same patient as Fig.* 1a *showing apparent capillary non-perfusion*

ANALYSIS

Patients were subdivided into four groups according to the site of occlusion:

1. Hemisphere vein occlusion
2. Main supero or infero-temporal vein occlusion
3. Macular vein occlusion

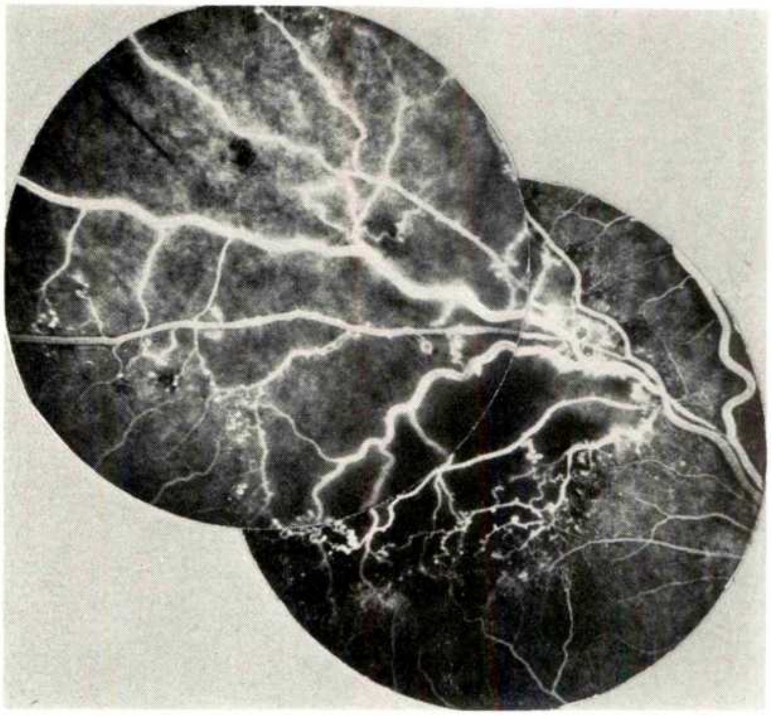
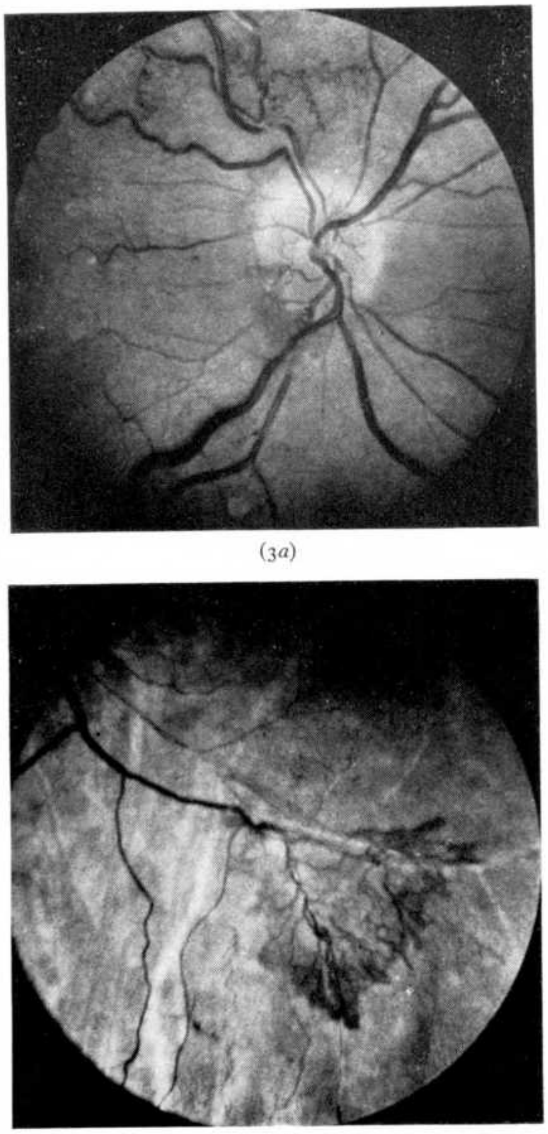


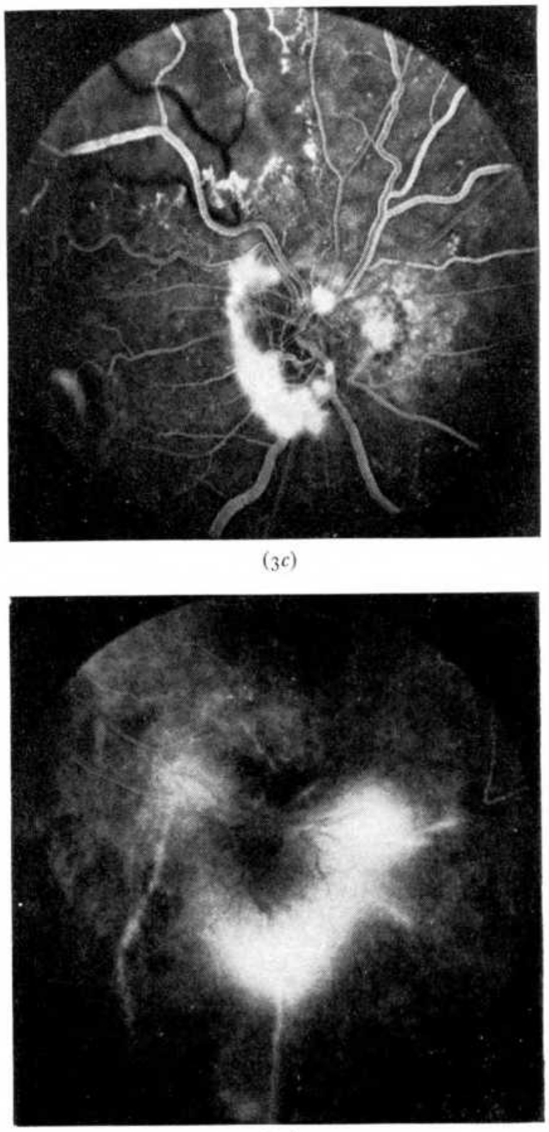
FIG. 2 *Fluorescein angiogram of a supero-temporal venous occlusion showing large areas of capillary non-perfusion*



(3*a*)

(3*b*)

FIG. 3(a), (b) *From a colour photograph of RBVO showing* (a) *disc, and* (b) *peripheral preretinal new vessels*



(3*c*)

(3*d*)

FIG. 3 (c), (d) *Fluorescein angiogram of* 3(a) *and* 3(b) *showing leakage of dye from the new vessels*

4. Peripheral vein occlusion.

No patient in the study was placed in group 4 as none had had visual symptoms within three months of occlusion because by definition the macula was not involved.

Patients were also subdivided according to which of the following was their most predominant feature: capillary closure, dilatation, or the presence or absence of new vessels.

The groups were compared statistically using Student's *t* test for unpaired samples when comparing numerical results (for example, blood pressure, plasma urea) and χ^2 test when comparing presence or absence of features in the various groups.

Results

There were eight patients with hemisphere occlusion, 37 with main supero-temporal or infero-temporal occlusion and 23 with macular occlusion. Table I shows that of the 68 eyes affected by

RBVO, there were 34 with pronounced capillary closure and 34 with capillary dilatation. While none of the eyes with predominant dilatation had new vessels, 21 of those with capillary closure had developed these lesions. The difference is highly significant ($P < 0.0001$).

Table II relates the site of occlusion with new vessel formation, capillary closure, and dilatation. No patient with macular RBVO had large areas of non-perfusion or new vessels, and only five of those with large branch vein occlusions had predominant dilatation. It is of interest that none of the patients with hemisphere occlusion developed new vessels.

Table III shows that in most patients new vessels occurred in the retinal periphery and there were only two patients who developed disc neovascularization without peripheral new vessels. Two-thirds of the patients with new vessels had at least one vitreous haemorrhage during the period of study (Table III), but no patient in this group suffered permanent loss of vision.

The early development of new vessels was a particularly interesting feature of this study.

A common finding seen on serial fluorescein angiograms was the ingrowth of blood vessels into the areas of non-capillary perfusion (Fig. 4). These vessels appeared to start as buds from the remaining vessels and to grow at right-angles to these vessels, later to branch and revascularize the retina. The growing tips of these vessels appeared dilated and leaked small amounts of fluorescein. Their distribution was dissimilar from the normal retinal vasculature indicating that the vessels were newly formed. These intraretinal vessels, however, failed to leak fluorescein extensively in contrast with the new vessels which lay in front of the internal limiting membrane of the retina.

Table I *Results in* 68 *eyes*

		New vessels	
Predominant feature	*No. of eyes*	*No.*	*Per cent*
Capillary dilatation	34	0	0
Capillary closure	34	21	62

Table II *Site of occlusion*

		Site of occlusion		
	No. of eyes	1	2	3
Closure and new vessels	21	—	21	—
Closure without new vessels	13	2	11	—
Dilatation	34	6	5	23

Table III *Site of new vessels and incidence of vitreous haemorrhage*

Site of new vessels	*No. of patients*	*Vitreous haemorrhage*
Disc only	2	2
Periphery only	15	10
Disc and periphery	4	2

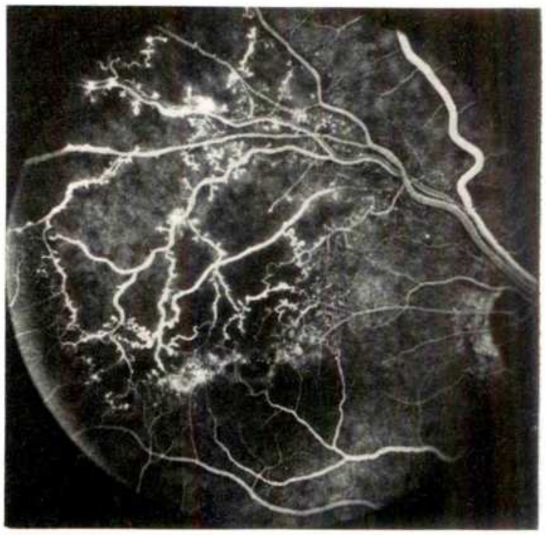


FIG. 4 *Fluorescein angiogram of the same patient as Fig. 2 seven months later showing revascularization of the non-perfused areas*

Table IV summarizes the medical findings. Patients with closure and new vessels (Group 1), closure and no new vessels (Group 2), and dilatation (Group 3) were compared. The results were similar in most features relating to general health, but when those without new vessels (Groups 2 and 3 together) were compared with those who had new vessels, the plasma urea and plasma uric acid levels were significantly higher in the latter group ($P < 0.05$).

Thirty-one of the 67 patients had diastolic blood pressure above 110 mmHg and a further nine were being treated for high blood pressure at the time of their examination although not at the time of the diagnosis of the vein occlusion. In a further eight patients there was electrocardiographic evidence of old infarction or atrial fibrillation, possibly accounting for normal blood pressure.

In only nine patients out of the 68 examined was there no evidence of arterial disease; the results of their cardiovascular examinations, electrocardiograms, and serum lipids were normal and they had no sign of diabetes. Seven of these had pronounced capillary dilatation.

Table IV *Medical findings*

Group (+ no.)	*Age (years) Mean (range)*	*Blood pressure* *Systolic (mmHg) Mean ± SE*	 *Diastolic (mmHg) Mean ± SE*	*Plasma urea (mg/100 ml) Mean ± SE*	*Plasma uric acid (mg/100 ml) Mean ± SE*	*Serum cholesterol (mg/100 ml) Mean ± SE*	*Serum triglyceride (mg/100 ml) Mean ± SE*	*Haemoglobin (g/100 ml) Mean ± SE*
1. Closure and new vessels (21)	59·95 (41–78)	180·2 ± 5·7	105·9 ± 2·6	* 39·4 ± 1·9	* 6·59 ± 0·33	220·1 ± 7·7	119·2 ± 14·9	14·4 ± 0·2
2. Closure without new vessels (13)	61·14 (48–79)	173·6 ± 7·5	100·0 ± 5·7	36·7 ± 2·0	6·14 ± 0·37	240·4 ± 10·1	164·9 ± 44·7	13·7 ± 0·5
3. Dilatation (34)	59·83 (27–72)	173·3 ± 4·1	102·3 ± 2·3	34·23 ± 1·5	5·00 ± 0·2	232·9 ± 7·1	117·9 ± 8·8	17·0 ± 0·3
4. (2 and 3 combined) No new vessels (47)	—	173·0 ± 3·6	102·1 ± 2·4	34·9 ± 1·3	5·61 ± 0·3	232·8 ± 5·9	130·7 ± 13·8	13·9 ± 0·2

*Significantly different from Group 4 (P <0·05)

Discussion

Neovascularization is common in many of the vascular retinopathies—for example, diabetes mellitus (Kohner, 1975), sickle cell disease (Goldberg, 1971), retinal periphlebitis (Eales, 1880; Asdourian, Goldberg, and Busse, 1975; Sanders and Shilling, 1976) and in various haematological disorders (Ring, Pearson, Sanders, and Wetherley-Mein, 1976).

The frequent occurrence of neovascularization after retinal branch vein occlusion is shown in this paper. Although its cause is as yet unknown there is evidence that 'hypoxic' retina in some way stimulates it (Wise, 1961; Ashton, 1961). Areas of capillary non-perfusion in the retina are ischaemic and probably hypoxic. Our finding that neovascularization occurs only in the presence of capillary non-perfusion strongly supports the ischaemic theory of neovascularization. Indeed there is a better correlation between capillary non-perfusion and neovascularization in branch vein occlusion than in most other retinopathies. It is interesting that peripheral non-perfusion of the retina appears to be the relevant factor and that central capillary non-perfusion does not seem to have the same stimulating effect, probably because the areas are not sufficiently large and diffusion may overcome the ischaemia.

The early development of new vessels into areas of non-perfusion is of interest and is similar to that demonstrated after experimental branch vein occlusion in monkeys (Hamilton, Kohner, Rosen, and Bowbyes, 1974). As shown both in animals and man there is very little dye leakage from these intraretinal new vessels and vitreous haemorrhage does not occur from them. A significant number of patients with preretinal new vessels had vitreous haemorrhages and this is therefore a serious complication of retinal branch vein occlusion.

It is of interest that levels of plasma urea and uric acid were higher in those patients with vascular occlusion and new vessels than in those without. Renal failure is associated with thrombosis in various veins, and in a group of 112 patients with central retinal vein occlusion Kohner and Cappin (1974) found three with chronic renal failure. In a recent publication (Ring and others, 1976) it was noted that viscosity was higher in those patients with vein occlusion (both central and branch) who had pronounced capillary closure. The exact cause of thrombotic episodes in renal disease is not known, nor do we know why some patients have predominant capillary closure. These findings should stimulate further work in both the pathogenesis of retinal vein occlusion and the cause of thrombotic episodes in chronic renal disease.

The main aim of this study was to help to determine the prognosis for an individual patient with RBVO and indicate lines of possible treatment and prophylaxis. First, we have shown that neovascularization does not occur secondary to small macular retinal branch vein occlusions. Secondly, fluorescein angiography after a vein occlusion will assess the presence of peripheral capillary non-perfusion and the possibility of late neovascularization may be predicted. There are important therapeutic implications from our findings. Ablation of peripheral ischaemic retina by photocoagulation has been used to treat new vessels on the disc, particularly in diabetes (Diabetic Retinopathy Study Research Group, 1976) and this also appears to be a rational form of treatment in the neovascular complications of branch vein occlusion by which means the ischaemic stimulus to neovascularization may be reduced. Although preretinal new vessels may be destroyed directly by photocoagulation, this is difficult with disc neovascularization and it is in the treatment of this complication that photocoagulation of the ischaemic quadrant of the retina may be the most effective form of therapy. The high incidence of neovascularization raises the possibility of reducing the chances of this complication by early photocoagulation of non-perfused retina.

We thank Miss Rita Clarke for secretarial assistance and Mr Rolf Sennhenn for preparing the illustrations.

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A prospective study of xenon arc photocoagulation for central retinal vein occlusion

DONALD R. MAY, MICHAEL L. KLEIN, AND GHOLAM A. PEYMAN
From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago, Illinois

The clinical symptoms of central retinal vein occlusion have been recognized for the past century. The disease was first described in 1855 (Liebreich, 1855), just five years after Helmholtz invented the ophthalmoscope. There have been many subsequent studies on its natural history and pathogenesis (Klien, 1953; Hayreh, 1971; Vannas and Raitta, 1972).

The treatment of central retinal vein occlusion has been controversial with a myriad of therapeutic modalities producing varying results in different hands. Therapeutic regimens including potassium iodide and pilocarpine (Braendstrup, 1950), irradiation (Gradle, 1937; Benedict, 1948; Hessberg, 1944), anticoagulants (Holmin and Polman, 1938; Klien and Olwin, 1956; Vannas and Orma, 1957), fibrinolytic agents (Dolenek, Blatny, and Navratil, 1968; den Ottolander, 1968), dextran 40 (François and Verbracken, 1974), corticosteroids (van Loon, 1961; Mehlan, Eichler, and Jenssen, 1974), and carbogen (95 per cent O_2, 5 per cent CO_2) (Sedney, 1976) have been advocated.

There have been reports of good results obtained with the use of photocoagulation in branch vein occlusion (Krill, Archer, and Newell, 1971; Campbell and Wise, 1973; Gitter, Cohen, and Baber, 1975) and diabetic retinopathy (Diabetic Retinopathy Study Group, 1976). Recently, reports of photocoagulation for central vein occlusion (François, Cambie, and De Lacy, 1974; Freyler and Nichorlis, 1974; Theodossiadis, Charamis, and Velissaropoulos, 1974; Wetzig and Thatcher, 1974; Zweng, Fahrenbrush, and Little, 1974; Oosterhuis and Sedney, 1975; Sedney, 1976) have also shown good results. To our knowledge there have been no previous controlled prospective studies.

This paper is a preliminary report on the first 20 patients in a prospective controlled study initiated three years ago by two of us (MLK and GAP) to evaluate the effect of xenon photocoagulation on central retinal vein occlusion.

Materials and methods

Patients over 40 years of age with central retinal vein occlusion and a visual acuity of 20/40 or less were referred to us from both the clinic and private patient populations. The purpose and nature of the study were explained to the patients. Patients being treated with medications such as anticoagulants, corticosteroids, or vasodilators specifically for the central vein occlusion were not included in the study. Patients with ocular diseases (for example, diabetic retinopathy) which could influence visual acuity and those whose ocular media were not clear enough to permit photocoagulation were also excluded.

A thorough medical history was taken and then each patient was referred to the Department of Medicine at the University of Illinois Medical Center for a thorough examination. All patients underwent laboratory tests including at least: a complete blood cell count, urine analysis, three-hour glucose tolerance test, plasma thromboplastin, partial thromboplastin time, haemoglobin electrophoresis, serum protein electrophoresis, electrocardiogram, chest *x*-ray, red blood cell sedimentation rate, and serum cholesterol and triglycerides.

A complete ophthalmological examination was performed including the following: visual acuity (Snellen chart, refracted), slit-lamp examination of the anterior segment, gonioscopy and fundus biomicroscopy, applanation tonometry, visual fields (Goldmann), fundus and iris fluorescein angiography, stereoscopic colour pictures of the fundus, and electroretinography.

The patients were randomly assigned to the treatment or non-treatment group by drawing pieces of paper labelled 'treat' or 'non-treat' from a bag. Those in the non-treatment group were given no therapy for the central vein occlusion and were followed-up every three months. Patients in the other group were treated as outpatients and given photocoagulation with the Zeiss xenon photocoagulator using a Fankhauser slit-lamp delivery system.

Topical 0·5 per cent tetracaine and retrobulbar 2 per cent lignocaine with epinephrine 1 : 100 000 and hyaluronidase were given before treatment. Through dilated pupils, an average of 214 lesions (3° centrally; all others 4·5°) with an average total energy delivery of

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Address for reprints: Donald R. May, MD, 1855 W. Taylor Street, Chicago, Illinois 60612, USA

169 joules were delivered as a 360° scatter photocoagulation in one treatment session. The lesions were placed at least 3° apart with no lesions placed within one disc diameter of the disc or fovea. In addition, focal treatment was applied to neovascularization from the retina (NVE) when present. Neovascularization from the disc (NVD) was not treated directly. A polymyxin B-bacitracin-neomycin ointment and an eye patch were applied to the eye after treatment and the patient was examined the next day, then every week for one month, and finally at three-monthly intervals.

Eleven of the 20 patients initially admitted to the study were randomly assigned to the non-treatment group and nine were treated. Table I shows the random allocation of the patients. For one patient in each group the follow-up period was three months or less.

Results

In the untreated group the visual acuity improved two lines or more on the Snellen chart in three eyes, decreased by two lines or more in four eyes, and remained unchanged in three eyes. In the treated group vision improved in one eye, decreased in two eyes, and remained unchanged in five eyes. One patient in each group did not have a long enough period of follow-up to assess the visual acuity changes. Table II lists the visual changes of each of the patients.

None of the eyes had NVD at the time of the initial examination. During the course of the study, however, NVD developed in two of the untreated and one of the treated group. One patient in the treated group had NVE initially. This was treated focally as described above, but NVE again developed in the same eye.

Rubeosis iridis was observed only in the untreated group. Two of the patients randomly assigned to the non-treatment group initially had rubeosis. Rubeosis developed in two additional patients in the untreated group and all four progressed to neovascular glaucoma. Rubeosis was initially seen on an average of 3·25 months after the patient's reported date of onset of visual symptoms. Of the untreated patients there were five with a significant disappearance of capillaries at the posterior pole on initial examination as demonstrated by fundus fluorescein angiography. Of these five patients, two had rubeosis on entering the study and two developed rubeosis subsequently. These four eyes later developed neovascular glaucoma. Four of the nine patients in the treated group presented with extensive disappearance of capillaries at the posterior pole on initial examination but none went on to develop rubeosis.

Table I *Summary of data on patients*

Patients	*Untreated*	*Treated*
Number	11	9
Mean age (years)	73 (52–88)	67 (50–76)
Glaucoma	5	4
Hypertension	5	2
Average time until examination (months)	4·5	4·25
Average follow-up (months)	19·5	15
Insufficient follow-up	1	1

Table II *Changes in visual acuity*

	Visual acuity	
Patients	*Initial*	*Final*
Controls		
1	3/200	10/200
2	Perception of light	20/300
3	2/200	2/200
4	2/200	No perception of light
5	20/400	*
6	Perception of light	No perception of light
7	Hand movements	Perception of light
8	Hand movements	Hand movements
9	20/400	20/70
10	20/70	No perception of light
11	20/400	20/200
Treated		
1	1/200	Hand movements
2	20/400	20/300
3	3/200	20/200
4	2/200	*
5	5/200	3/200
6	3/200	3/200
7	6/200	2/200
8	20/400	20/300
9	8/200	No perception of light

*Insufficient follow-up

Discussion

Photocoagulation has been advocated for vascular diseases of the retina including branch vein occlusion and diabetic retinopathy. The current rationale is that the destruction of hypoxic tissue by photocoagulation reduces the vascular load on the posterior pole, decreasing macular oedema and capillary leakage and allowing the remaining tissue to receive an adequate blood supply (Campbell and Wise, 1973; Theodossiadis and others, 1974). Furthermore, destruction of the pigment epithelium may promote diffusion of fluid into the choroid (Peyman, Spitznas, and Straatsma, 1971). It is also felt that the reduction in hypoxic tissue decreases the neovascular stimulus on the globe (Krill and others, 1971; Cleasby, Hall, Fung, and Webster, 1974).

From the analysis of our preliminary data we find no significant differences between the two groups regarding visual prognosis. Our data also currently show no definitive effect on posterior pole neovascularization.

The only effect of scatter photocoagulation found in our study was the prevention of rubeosis iridis and subsequent neovascular glaucoma. Four of the untreated group developed neovascular glaucoma although two of these patients had rubeosis when they were randomly assigned to the non-treatment group. None of the patients in the treated group has developed neovascular glaucoma. Between 8 and 48 per cent of patients with central vein occlusion are reported to develop neovascular glaucoma ultimately (Gradle, 1937; Braendstrup, 1950; Vannas and Orma, 1957; Raitta, 1965). Our preliminary data show that 360° scatter treatment with xenon photocoagulation may be significant in the prevention of neovascular glaucoma.

Summary

Twenty patients with central retinal vein occlusion were randomly divided into two groups in a prospective study to evaluate the effects of xenon arc photocoagulation in central retinal vein occlusion. The patients in one group were treated with 360° scatter xenon photocoagulation and the others received no treatment. The average follow-up was 18 months. There were no cases of rubeosis or neovascular glaucoma in the treated group. Two patients in the untreated group developed rubeosis with subsequent neovascular glaucoma. There was no significant difference in the visual prognosis or in fundus neovascularization between the groups.

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Laser induced phagocytosis in the pigment epithelium of the Hunter dystrophic rat

P. L. ANSELL AND JOHN MARSHALL
From the Department of Visual Science, Institute of Ophthalmology, London

The membrane systems in the outer segments of rod photoreceptor cells in the retinae of normal rats are in a state of flux. The bimembranous discs of which the outer segment is composed (Pedler and Tilly, 1967) are continuously being renewed throughout life (Young, 1967). New discs are formed in the region of the inner segments of the receptor cell and are progressively displaced towards the pigment epithelium by successive disc production. The time taken for a newly-formed rat disc to traverse the outer segment is about nine days (LaVail, Sidman, and O'Neil, 1972). Old discs at the tips of rod outer segments are removed by the phagocytic action of the pigment epithelium (Young and Bok, 1969). The spent discs are engulfed by the epithelial cell in groups of varying numbers, but at a rate which approximately equals the rate of production. Thus in adult animals no marked change in receptor length is recorded. Once inside the pigment epithelium the groups of discs, called phagosomes, undergo lysis which results in their progressive degeneration (Marshall, 1970a; Ishikawa and Yamada, 1970; Marshall and Ansell, 1971).

Morphological studies on the retinae of rats with retinitis pigmentosa have shown the presence, and progressive accumulation, of membranous material between the outer segments of the retinal receptor cells and the pigment epithelium (Dowling and Sidman, 1962). This extracellular material has been shown to originate from the spent discs of receptor cells (LaVail and others, 1972). It has also been demonstrated experimentally that the accumulation of receptor debris is not related to an increased rate of production of rod discs (Herron, Riegel, Myers, and Rubin, 1969), but to the absence of uptake of this material into the retinal pigment epithelial cells (Bok and Hall, 1971). These findings have led to the conclusion that in rats with retinitis pigmentosa a malfunction exists in the phagocytic relationship between the receptor cells and the retinal pigment epithelium. Such a breakdown could arise from anomalies inherent in either the receptor cell or in the pigment epithelium. Several workers have demonstrated that the pigment epithelium of these animals contains the lytic enzymes capable of inducing phagosome degradation (Burden, Yates, Reading, Bitensky, and Chayen, 1971; Ansell and Marshall, 1974). Thus either the spent rod discs are altered in some way and hence the pigment epithelium will not engulf them, or the apical membrane of the pigment epithelium is at fault and will not allow the spent discs to pass through. Some biochemical anomalies have been found in the outer segments of these animals; for example, Schmidt and Lolley (1973) and more recently Dewar, Barron, and Richmond (1975) showed that the retinae of mice and rats with retinal dystrophies are deficient in the enzyme, retinal phosphodiesterase. It has been suggested that the resultant accumulation of cyclic nucleotides—such as, adenosine 3′, 5′ monophosphate and guanosine 3′, 5′ monophosphate—could result in the changes associated with the anomalous photoreceptor differentiation and function (Farber and Lolley, 1974; Dewar, Barron, and Reading, 1975), although further work on the Royal College of Surgeons (RCS) rat suggests that these changes are secondary and related to the accumulation of photoreceptor debris (Lolley and Farber, 1976). There is now increasing evidence that the phagocytic process of the pigment epithelium is discriminatory (Hollyfield and Ward, 1974a, b). Thus in dystrophic animals the lack of phagocytosis may be caused by the receptors presenting the wrong signal to the apical membrane of the pigment epithelium. Corroborative evidence for this hypothesis has been obtained recently in two separate experimental investigations (Reich-D'Almeida and Hockley, 1975; Custer and Bok, 1975). Both these groups of workers injected substrate material into the subretinal space of dystrophic rats, the former used carbon particles while the latter employed photoreceptor outer segment fragments isolated from normal rats. In both series of experiments the substrate particles were engulfed by the pigment epithelium of the dystrophic animals and appeared as membrane-bound inclusions. The

Address for reprints: Dr J. Marshall, Department of Visual Science, Institute of Ophthalmology, Judd Street, London WC1H 9QS

phagosomes of outer segment material described by Custer and Bok (1975) were identical with those found in normal animals.

In normal animals if the retina is experimentally damaged either by laser irradiation (Marshall, 1970a; Marshall and Mellerio, 1970) or by ischaemia (Johnson, 1975) the endemic phagocytic activity of the pigment epithelium becomes hyperactive and clears the debris from the damaged site. In contrast with ischaemia, lasers produce a controlled localized area of damage. At the centre of the irradiated area many pigment epithelial cells and their associated receptor outer segments experience a great increase in temperature and therefore become thermally denatured (Marshall, 1970b). However, in the peripheral zone of the lesion the epithelial cells recover from any transient thermal insult and begin to form new cells, many of which dissociate from Bruch's membrane and assume the activity of wandering macrophages (Marshall and Mellerio, 1970).

The current paper reports the induction of phagocytosis in the pigment epithelium of retinitis pigmentosa rats by exposing them to low-power laser irradiation of the retina. It is not a therapeutic proposal.

Methods and materials

To ensure that laser energy was absorbed in the region of the pigment epithelium, pigmented dystrophic animals (Hunter strain) were used throughout this study.

To achieve maximum mydriasis 2 drops of 1 per cent cyclopentolate were instilled into one eye of each 14-day-old rat. After 20 minutes the animals were anaesthetized with diethyl ether and then the eye was exposed to an experimental pulsed ruby laser system mounted on a Zeiss slit-lamp (Perkins and Brown, 1973). The system used a 5·1 cm × 6·4 mm (2 × ¼ in) ruby rod which was air cooled and had a pulse duration of 450 μs. The laser beam passed through auxilliary optics and and was brought to a focus coaxially with the illumination beam of the slit lamp. The output energy of the laser was adjusted to between 5 and 30 mJ by introducing glass neutral density filters into the beam path. Beam power levels were monitored on a model 42 calorimeter (Laser Associates Ltd) and displayed on a model 155 voltmeter (Keithley Instruments).

To locate lesions in specific positions on the rat's fundus, the refractory system of the rat's eye was negated by pressing a cover slip on its cornea. Three lesions were produced in one eye of each animal, and in each case these were located away from the optic disc or major vessels.

The animals were killed with chloroform on the fifteenth postoperative day, and their eyes were immediately removed. After a corneal incision each eye was immersed in 15 ml of 2·5 glutaraldehyde buffered to pH 7·4 in 0·1 mol/l sodium cacodylate containing 10 mg/ml calcium chloride. Five minutes after immersion in this fixative a circumferential incision was made just posterior to the sulcus sclerae, and the anterior part of the eye, together with the lens and vitreous, were discarded. After a total fixation time of 20 minutes the lesions together with unirradiated control areas were isolated from the posterior eye cups using a dissecting microscope. Samples were then processed for light and electron microscopy or electron histochemistry as previously described (Ansell and Marshall, 1974).

Results

The morphology and acid phosphatase distribution in control areas of dystrophic retina were similar to those previously described (Ansell and Marshall, 1974), but in addition in the present series of experiments lead phosphate deposit indicating acid phosphatase activity was found over lysosomes within the pigment epithelium (Fig. 1*a*).

In light microscopical examination of the pigment epithelium the irradiated areas could clearly be distinguished. The cytological appearance varied both with the irradiance of the initial exposure and with the distance of individual cells from the centre of the irradiated area.

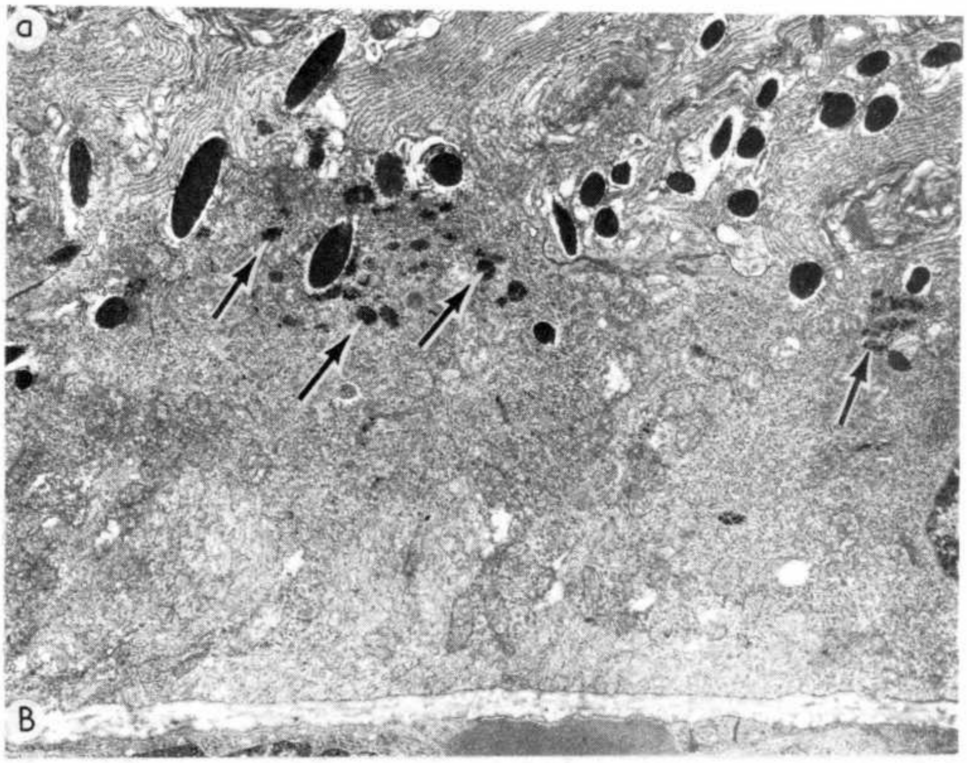
In the higher energy exposures (10 to 30 mJ) Bruch's membrane was deformed, multilayered, and enlarged in thickness, and often contained globular lipid-like inclusions.

In all exposures the entire area of the lesion was covered by pigment epithelial cells (Fig. 1*b*). These proliferated epithelial cells were either flattened and elongated (size 20 × 5 μm) or rounded and globular (size 15 μm). The flattened cells were spindle-shaped and maintained contact with Bruch's membrane over a large part of their basal surface area (Fig. 2*a*). In contrast, the globular cells projected into the outer segment region of the photoreceptor cells and were either separated from Bruch's membrane, or associated over a limited area of their circumference sometimes only by villiform projections (Fig. 2*b*). In the periphery of many lesions, rounded pigmented cells could be seen between normal pigment epithelial cells attached to Bruch's membrane, and the outer segments of photoreceptor cells (Fig. 2*c*). In other lesions within the central area a hyperplasia of the epithelial cells was observed, and consisted of successive layers of spindle-shaped poorly pigmented cells.

In low-energy exposures (5 to 10 mJ) the epithelial cells within the irradiated areas were irregular and either larger or smaller than those in control sections. Few cells were seen isolated from Bruch's membrane.

In all lesions the layer of subretinal photoreceptor debris normally found in these animals was either reduced or removed (Figs 1*b*, 2).

In both mild and severe lesions the various types of epithelial cells were seen to contain densely



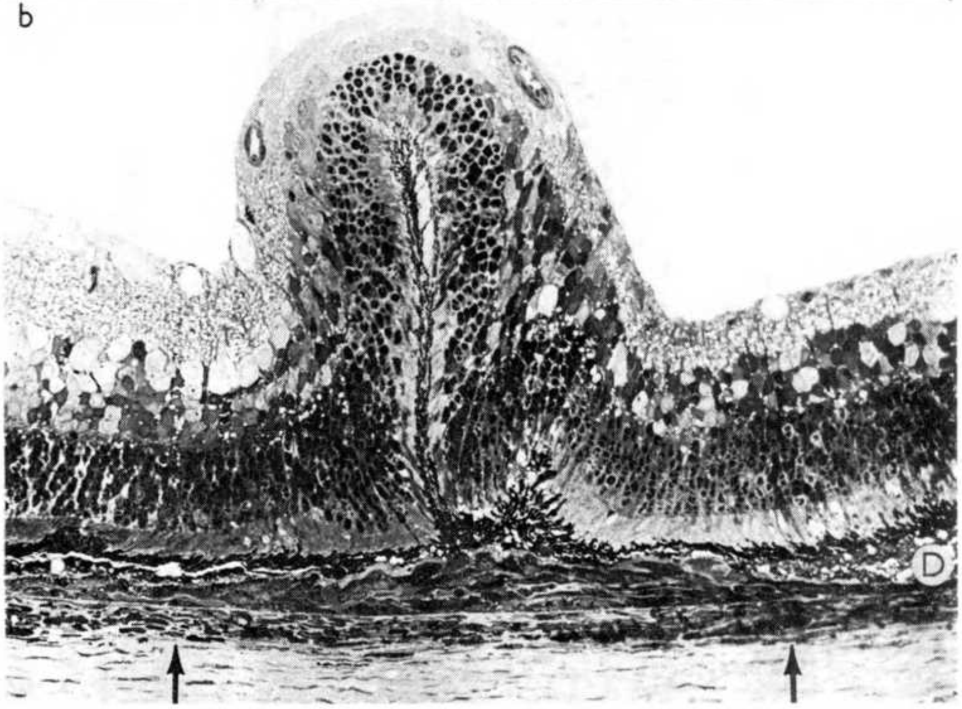


FIG. 1*(a)* *Electron micrograph of dystrophic rat pigment epithelium with lead phosphate deposits over lysosomes (arrowed), indicating presence of acid phosphatase: Bruch's membrane (B).* ×8400

FIG. 1*(b)* *Light micrograph of centre of a 15-day-old laser-induced lesion in retina of a dystrophic rat. Regenerated pigment epithelial cells are present throughout irradiated area (arrowed), and are associated with a reduction of debris (D) in the subretinal space.* ×560

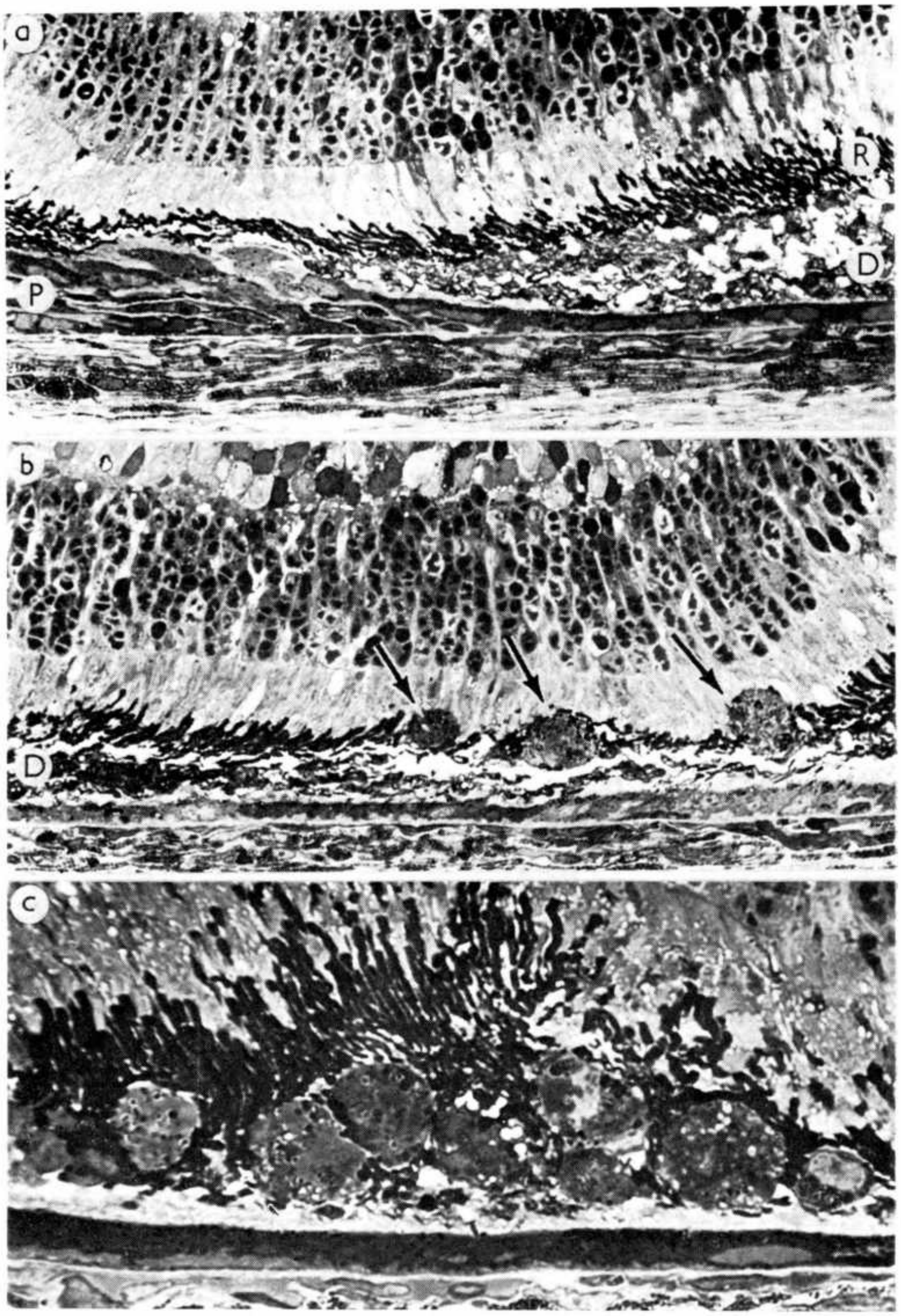


FIG. 2 *Light micrographs of receptor epithelial junction in areas of dystrophic rat retina irradiated with laser light.* (a) *The subretinal debris (D) is lost over the multi-layered proliferated epithelial cells (P). Photoreceptor cell outer segments (R) are present throughout irradiated area.* × 560. (b) *Globular regenerated epithelial cells (arrowed) in a subretinal space at edge of a laser lesion.* × 560. (c) *Proliferated epithelial cells containing phagosomes, at centre of a small laser lesion.* × 1240

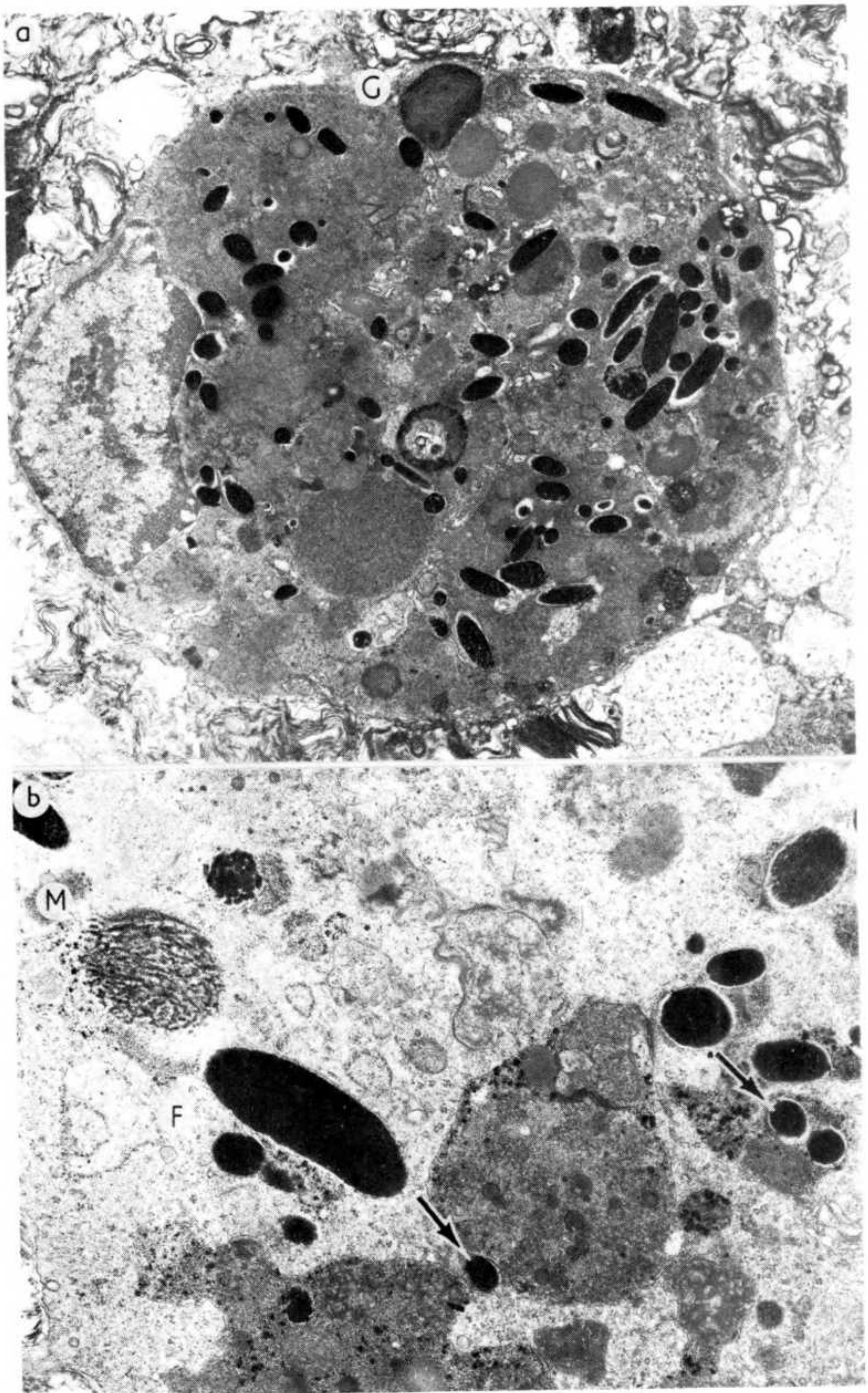


FIG. 3 (a) *Electron micrograph of regenerated epithelial cell in the subretinal space. Cell contains phagosomes (G) and both free and engulfed melanin granules.* ×8000. (b) *Electron micrograph of organelles and inclusions in a regenerated epithelial cell: free melanin granules (F) and premelanosome (M), ingested melanin granules (arrowed).* ×20 000 staining inclusions with the size and appearance of phagosomes.

On examination of the irradiated areas in the electron microscope the proliferated pigment epithelial cells had a substructure similar to that of normal retinal epithelial cells. They were seen to contain numerous organelles, including many associated with the normal development of pigment granules—for example, premelanosomes and mature melanin granules (Fig. 3). In some cells similar organelles were also found in groups or together with amorphous material within membrane-bound systems. In histochemical samples these membrane-bound inclusions were always associated with dense lead phosphate precipitates. Many cells contained engulfed particles of photoreceptor outer segments and these were similar to but larger than those found in the pigment epithelium of normal rats (Figs 3, 4). The rounded cells that had separated from Bruch's membrane usually contained greater numbers of phagosomes per cell than the spindle-shaped variety. In some few cases the active incursions of the bounding membrane of epithelial cells into receptor cell debris were observed.

In the samples taken from areas of irradiated retina tested for acid phosphatase activity, lead phosphate deposits were seen over the phagosomes and presumptive lysosomes (Figs 4*b*, c). The intensity of the reaction varied with both the appearance and position of the phagosome. Peripheral inclusions with relatively unaltered membrane structure always had less lead deposit than the more central and disorganized structures. In contrast with the unirradiated areas little reaction product was seen associated with either the bounding membranes or the extra cellular debris.

In the areas of the lesion some receptor cells were destroyed and degenerating remnants of the inner portions of these cells were identified by their electron-dense staining. Occasionally photoreceptor cells in the periphery of the irradiated area were seen to contain phagosome-like material within their inner segments (Fig. 5).

Discussion

The pigmented cells observed in the irradiated areas of dystrophic rat retinae are similar to the proliferated epithelial cells described in other animals exposed to similar sources of radiation. In most animals the epithelial cells adjacent to the damaged area flatten and then extend along Bruch's membrane and into the lesion. These amoeboid processes coupled with new cells derived from either budding (Marshall and Mellerio, 1970) or mitotic division (Gloor, 1969) result in a re-epithelialization. In many instances the newly formed cells bud off from Bruch's membrane when they reach the centre of the lesion (Marshall, Frankhauser, Lotmar, and Roulier, 1971). The resultant wandering cells always contain large numbers of phagosomes (Fig. 3). In a study of phagocytic activity of the pigment epithelium of the frog *(Rana pipiens)* using pasteurized bacteria, large phagocytic cells were observed within the subretinal space, but the authors concluded that these were probably blood-borne leucocytes (Hollyfield and Ward, 1974a). This deduction was based on observations of differences in subcellular morphology and the fact that melanosomes were absent. Similar observations were used to discriminate between two populations of cells in studies on the salamander (Keefe, 1973), and on the rabbit (Marshall and others, 1971). Both these studies concluded that most of the wandering cells within the subretinal space were derived from the pigment epithelium, while a small number may be derived from the blood. In the current study most cells in the subretinal space contained normal premelanosomes and pigment granules and had an endoplasmic reticulum identical with that of pigment epithelial cells in unirradiated areas. We conclude, therefore, that most phagocytic cells within the irradiated areas of dystrophic rat retinae are of epithelial origin.

Several papers confirm the presence of a discriminating recognition process in the phagocytic mechanism of the pigment epithelium (Hollyfield and Ward, 1974a; Reich-d'Almedia and Hockley, 1975; Custer and Bok, 1975; Hollyfield, 1976). These workers showed that the pigment epithelium will ingest carbon particles and latex spheres, will not ingest pasteurized bacteria, and has difficulty in engulfing normal receptor outer segments prepared by subcellular fractionation. Clearly the pigment epithelium is relatively omnivorous for abiotic particles, but must possess a fine sensory mechanism to discriminate between a normal spent section of rod outer segment and one that has been subjected to *in vitro* isolation techniques.

The omnivorous response to inert particles suggests that the process of ingestion may not require a specific chemical induction system to activate the apical membranes of the pigment epithelium, as it is unlikely that carbon particles or latex spheres possess such systems. It has been stated that the surface charge of these particles may be important in the recognition process (Karnovsky and Wallach, 1963) as the charge on latex spheres is the same but of twice the magnitude as that of biological membranes (Feeney and Mixon, 1976). However, amorphous carbon particles have no net charge and are still readily engulfed. These observations imply that the membrane receptor sites of the pigment epithelium are non-specific, but that they possess an active rejection system when confronted with potentially harmful material.

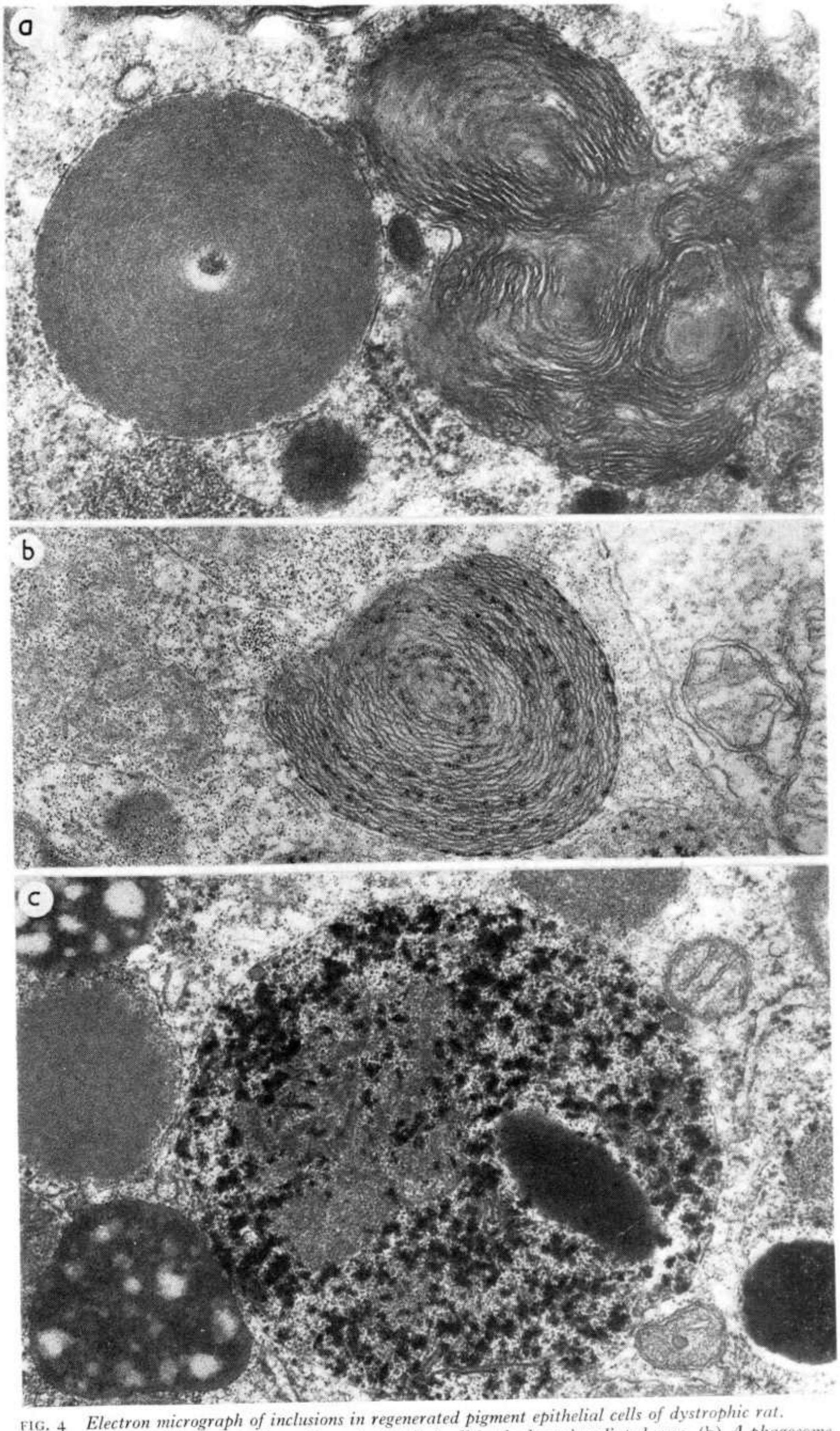


FIG. 4 *Electron micrograph of inclusions in regenerated pigment epithelial cells of dystrophic rat.* × 50 000. (a) *Phagosomes within a pigment epithelial cell in the laser irradiated area.* (b) *A phagosome associated with lead phosphate deposits indicating acid phosphatase activity.* (c) *A dense lead phosphate deposit associated with a phagocytic inclusion containing both amorphous debris and a melanin granule*

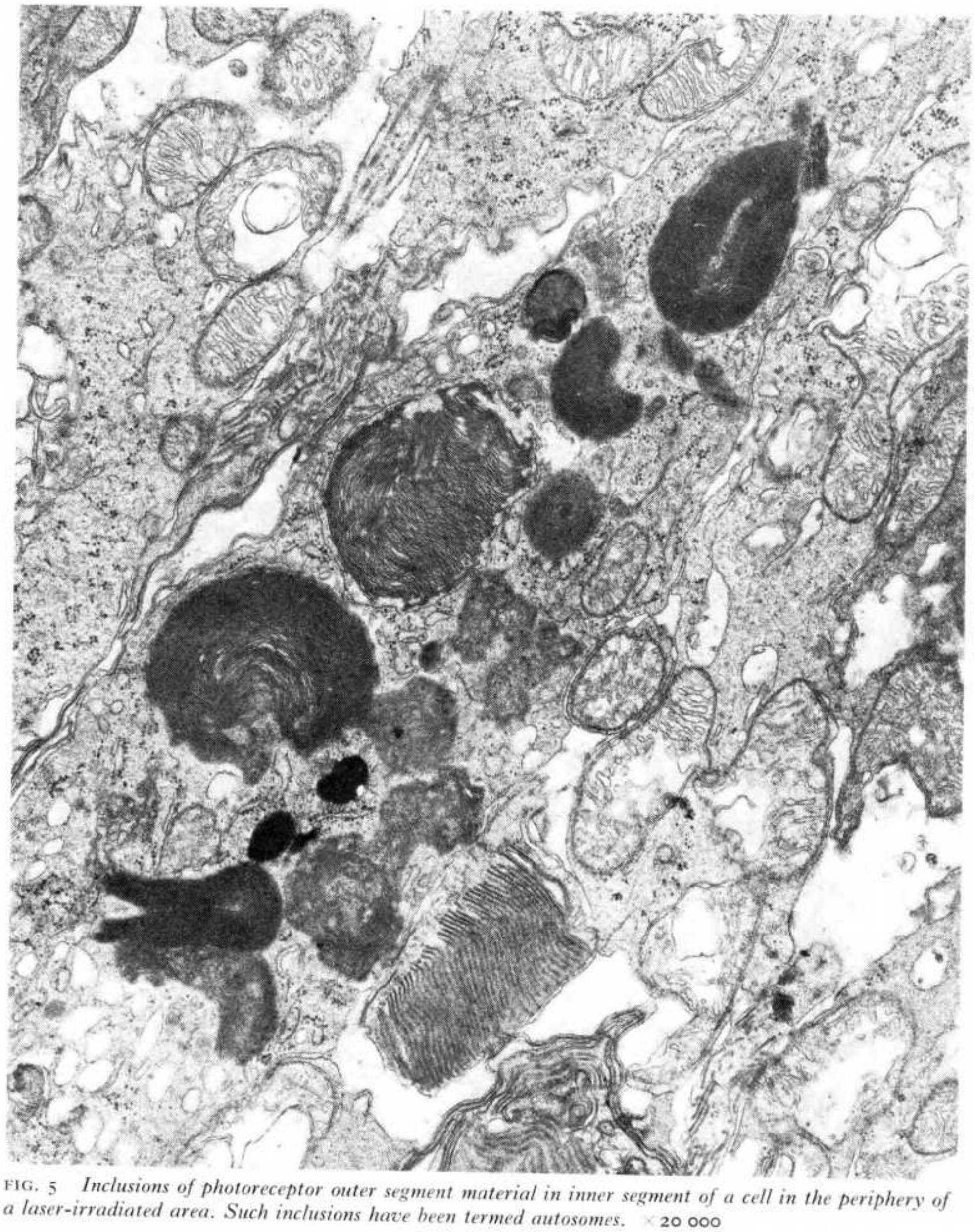


FIG. 5 *Inclusions of photoreceptor outer segment material in inner segment of a cell in the periphery of a laser-irradiated area. Such inclusions have been termed autosomes.* ×20 000

In the current study the debris from both damaged photoreceptor and pigment epithelial cells was ingested and shown to be in association with lytic enzymes. Pigment granules and premelanosomes are readily recognized as morphological entities within the boundary membranes of phagocytic particles. However, the appearance of membranous 'whirls' and their exclusive identification as phagosomes of outer segment material is difficult as such structures are characteristic of degenerating or damaged cells and have been observed in many systems (Meban, 1972; Tripathi and Ashton, 1976). In some instances the morphology of the phagosomes observed in the present study was such that their photoreceptor origins could be determined. The lipid-like deposits within Bruch's membrane suggest that there is some resistance to voiding the breakdown products of lysis and that there may be an imbalance in blood retinal exchange. However, this probably arises because of the thickening of Bruch's membrane and the loss of choroidal capillaries within the irradiated area in severe exposures.

The observation of phagosomal particles within the inner segment region of some photoreceptors in the periphery of the irradiated area may relate to the recent findings of Reme and Young (1976). These authors describe such particles called autosomes in the cones of the ground squirrel during the loss of these receptors before hibernation. Observations in our laboratory show autosomal inclusions in cones to be characteristic of degenerative changes associated with both traumatic insult and ageing. The sparse distribution of cells with such inclusions in the present study could reflect a cone-like receptor population in rats (Leure-du Pree, 1971).

Clearly the changes induced in photoreceptor and pigment epithelial cells as a result of laser irradiation removes the influence that precludes phagocytosis in the Hunter rat.

The proliferated epithelial cells must have the same genetic complex as their parent cells and therefore it would be difficult to consider them having significantly different biochemistry. In contrast the receptor cell outer segments within the irradiated area have been thermally denatured.

There are four primary mechanisms by which the morphological manifestations observed in dystrophic rats could arise (Custer and Bok, 1975).

1. The pigment epithelium lacks some component necessary for phagocytosis.
2. The rod outer segment either lacks an essential inducing agent, or possesses an inhibiting agent that precludes phagocytosis.
3. Both the above mechanisms are present in some combination and collectively contribute.
4. Complementary defects are present in the rod outer segment and the pigment epithelium and the disease manifestations are expressed only when both defects are combined.

The results reported in this paper, together with the reports of Custer and Bok (1975) and Reich-D'Almeida and Hockley (1975), strongly suggest that the primary lesion is in the photoreceptor cell (as in 2 above), and that this subsequently inhibits the phagocytic action of the pigment epithelium. However, the unilateral evidence of these studies has recently been countered by observations on a chimeric rat produced by the aggregation of embryos of albino dystrophic animals with those of pigmented normal animals (Mullen and LaVail, 1976). The resulting animals had mosaic eyes with both pigmented and non-pigmented epithelium. Degeneration of the photoreceptor cells occurred only in patches opposite areas of non-pigmented, dystrophic pigment epithelium, and the authors concluded that the primary lesion was confined to the pigment epithelial cell (as in 1 above). It is difficult to justify these observations with those of the current paper or previously published reports. However, two further possibilities must be considered. First, it is not known whether the dystrophic cells within the neural retina always come to lie adjacent to dystrophic pigment epithelium. Clearly the initial separation of these two layers and the temporal sequence of invagination and differentiation of the neural retina render this hypothesis unlikely. However, an inductive system may be present, and in the absence of markers for dystrophic photoreceptor cells, it cannot be ignored. Secondly, a primary malfunction in the pigment epithelium which is part of the blood retinal barrier may also give rise to problems in receptor homeostasis which in turn could preclude phagocytosis (as in 3). While the first of these two suggestions is unlikely, the last would explain the anomalies which now exist in the literature.

Summary

The retinae of 14-day-old Hunter dystrophic rats have been subjected to low-energy irradiation by a pulsed ruby laser. Fifteen days after exposure, pigment epithelial cells had proliferated and repopulated the irradiated areas. In all such areas the subretinal photoreceptor debris had been reduced or lost.

We would like to thank Dr Celia Yates for the donation of a breeding pair of pigmented dystrophic rats and Miss Sally Moore for maintaining the breeding stock. The electron microscope used in this study was a gift from the Wellcome Foundation.

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Vitreoretinal reactions and persistent hyaloid vessels

FRITZ H. STEFANI AND W. ANNA LASZCZYK*
From the University Eye Hospital, Munich

In the large series of cases of pseudoglioma reported by Howard and Ellsworth (1965) the conditions of persistent hyaloid vessels (PHV) or persistent primary vitreous (PPV) often occurred as a single anomaly, but only rarely as part of a syndrome—for example, Reese's dysplasia, Heine-Norrie's disease, incontinentia pigmenti Bloch-Sulzberger, Laurence-Moon-Bardet-Biedl's syndrome, chromosomal anomalies of group D.

Retinal changes may be combined with PHV and PPV—that is, with retinal folds (Mackensen, 1953), falciform retinal detachment (v. Barsewisch, 1968), areas of chorioretinal atrophy (Gloor, 1975), or atypical retinal detachment (Gloor and Haller, 1968). Retinal dysplasia is a lesion more often found in association with complex anomalies; Ricci (1969) used the term vitreoretinal dysplasia for such cases.

Vitreoretinal adhesions (Mann, 1935) have been shown experimentally to occur as a developmental anomaly (Orts Llorca and Genis Gálvez, 1960). Tripathi and Ashton (1971) found that vaso-glial connexions were normal in the adult rabbit. Vitreoretinal strands in man are regarded as being degenerated vitreoretinal anastomoses of blood vessels (Hagedoorn and Sieger, 1956; Reese, 1955; Wolter and Flaherty, 1959; Spaulding and Naumann, 1967; Gärtner, 1964). These strands are also seen in cases of non-oxygen induced retinitis proliferans in full-term infants (Stefani and Ehalt, 1974). The observation that retinitis proliferans occurs with other anomalies (Krümmel and Rausch, 1955; Benedikt and Ehalt, 1970; Addison, Font, and Manschot, 1972; Stefani and Ehalt, 1974; Best and Rentsch, 1974) is of importance regarding the mechanism of lesions that histologically mimic retrolental fibroplasia but which occur in children who have not received oxygen treatment, and of possible significance in understanding the mechanism that leads to fibroplasia.

We have records of only eight cases of PPV, relatively few compared with other hospitals (Manschot, 1958; Font, Yanoff, and Zimmerman, 1969; Jensen, 1968), but these are sufficient to advance some views of vitreoretinal reactions induced by persistent vascularized tissue within the eye; in cases which mimic retrolental fibroplasia the blood vessel formation was of especial interest.

Material

Each of the eight cases had been full-term and only one infant (Case 4) had received oxygen treatment because of cyanosis (Table I). The particulars of the clinical and macroscopical findings are given in Table II. Case 4 was clinically suggestive of 13–15 trisomy. The diagnosis of PPV was not made clinically.

HISTOLOGICAL FINDINGS (Table III)

Persistent primary vitreous (PPV)

The appearance of PPV varied considerably from loose cellular forms similar to normal (embryonic) primary vitreous (Cases 1, 2, and 3) to firm fibrous or scarlike forms (Cases 4, 5, 6, and 8). One (Case 7) showed a fatty transformation and another (Case 4) contained nests of chondroid tissue. The cellular form contained mainly two cell types, of fibroblastic and macrophagic vitreo-cystoid elements arranged in a netlike pattern. In a few sections in Case 1, a large intracellular periodic acid-Schiff-positive globule resembling a corpus amylaceum could be seen, but it was not possible to classify the surrounding cell. This cellular form of PPV was usually well vascularized while the fibrous form showed only poor vascularization, as did the form showing fatty degeneration.

Persistent hyaloid vessels (PHV)

Not all cases showed an obvious or patent persistent hyaloid artery (PHA) or vasa hyaloidea propria. Signs of obliteration of the PHA (thickening of the tunica intima and delamination of the internal elastic membrane with narrowing of the lumen) were not seen. The hyaloid blood vessel system was particularly prominent in Cases 1 to 3. Patent anastomosing vitreoretinal blood vessels were present in Cases 1, 2, 4, and 8 (Fig. 1). There were some glial cells sheathing the preretinal portion of the blood vessel anastomoses and prominent vitreoretinal strands were usually observed near by in these cases. These vitreoretinal strands consisted of a cellular (glial) portion on the retinal side which became fibrillary towards the vitreous. In some there were signs of traction along the strands with formation of retinal folds

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Address for reprints: Dr F. Stefani, Augenklinik der Universität München, 8 München 15, Mathildenstrasse 8, W. Germany

Table I *General clinical findings in eight cases*

Case (no.)	*Sex*	*Age*	O_2	*Other eye*	*Other clinical malformations*	*Other clinical findings*	*Cause of enucleation*
1	Boy	1 month	–	Normal	—	—	Hydrophthalmus
2	Girl	3 months	–	Normal	—	Grandmother 47 years old, myopic; mother 22 years old, myopic with peripheral retinal degeneration, holes and marked pupillary membrane; aunt 23 years old, myopic; uncle 14 years old, myopic with peripheral retinal degeneration and retinal holes	Suspected retinoblastoma
3	Boy	4 months	–	Normal	—	—	Suspected retinoblastoma
4	Girl	1 month	+	Cryptophthalmus	Cardioversion, hypoplasia of the lungs intestinal abnormalities	Cyanosis, death due to pneumonia	Necropsy
5	Boy	13 years	–	Normal	—	—	Secondary glaucoma
6	Boy	6 months	–	Normal	—	Maternal bleeding at 4 to 6 months	Suspected retinoblastoma
7	Boy	4 years	–	Normal	—	—	Hydrophthalmus
8	Boy	5 years	–	Normal	—	—	Suspected intraocular tumour

Table II *Clinical and macroscopical findings in enucleated eyes*

Case (no.)	*Clinical findings*	*Macroscopical findings*
1	Hydrophthalmus Corneal clouding Cataractous lens	Large globe Intracorneal filtering bleb (due to partial absence of Descemet's membrane) Small cataractous lens with calcification PHV and PPV Tunica vasculosa lentis
2	Microphthalmus Cataractous lens	Small globe Cataract, posterior lenticonus Total retinal detachment
3	Leucocoria	Total retinal detachment Iridocorneal adhesions Pre- and intraretinal haemorrhages
4	Suspected cryptophthalmus or anophthalmus	Cryptophthalmus, marked microphthalmus Sclerocornea Obliterated anterior chamber Small cataractous lens with calcification Connective tissue with chondroidal deposits in front of the folded nasal retina
5	Cataractous lens since birth Glaucoma Hyphaema	Cataractous, partly calcified lens, falciform retinal detachment nasally with adhesion to the lens
6	Microphthalmus Sclerocornea Leucocoria	Small globe Aphakia Suspected ciliary and optic coloboma Retinal detachment
7	Hydrophthalmus Leucocoria	Large globe Fatty tissue in the posterior chamber area (PPV?)
8	Microphthalmus Choroidal coloboma Cataract	Small globe Choroidal coloboma Cataractous lens PPV Total retinal detachment

(Fig. 2). Sometimes there was a close spatial relationship of PHV to the retina (Fig. 3) which was avascular in these areas. In three (Cases 2, 3, and 8) there was new vessel formation on the surface of an avascular retinal area (Fig. 4); there were no intraretinal glomeruloid endothelial proliferations suggestive of proliferation of retinal vessels but there were connexions to the vasa hyaloidea propria.

Retinal vascular changes

The avascular retinal areas were present mainly in the temporal periphery (Cases 1 to 4, and 8), although there was an avascular retinal area on the nasal side in some cases. In two cases, the vascular system was hypoplastic—for example, smaller blood vessels with wide intercapillary spaces. In the case of falciform retinal detachment there was a marked fibrosis of blood vessels in the area of attachment. In only one case did the retinal vascular system appear normal. In three eyes with peripheral temporal avascular retina, there were the already described new vessel formations on the retinal surface of these areas.

Structural retinal changes

Changes of the retinal structure were mainly due to loss or rarefaction of ganglion cells or microcystoid degeneration. Other changes present were various degrees of gliosis, retinal dysplasia, or cystic retinoschisis. Retinal fold formations by contracted vitreoretinal strands have already been mentioned.

Associated ocular changes

There were other changes associated with these cases of PPV—for example, hypoplasia of the anterior segment, cataracts and colobomata—but these are mentioned here only for the sake of completing the histological findings.

Table III *Histology of vitreoretinal changes in eight cases*

Case (no.)	*PHV*	*PPV*	*Vitreoretinal anastomoses of blood vessels*	*Proliferating preretinal blood vessels*	*Retinal vascular changes*	*Changes in retinal structure*
1	+	+ (Anterior and posterior)	–	–	Peripheral temporal retina with avascular areas	Rarefaction of ganglion cell layer Microcystoid degeneration at the posterior pole
	+	+ (Anterior and posterior)	+	+	Peripheral nasal and temporal retina with avascular areas	Retinal folds Microcystoid degeneration Ganglion cell layer rarefaction Gliosis
3	+	+ (Anterior and posterior)	?	+	Peripheral nasal and temporal retina with avascular areas	Intraretinal haemorrhages Microcystoid degeneration Loss of ganglion cells Gliosis
4	+ (No obvious persistent hyaloid artery)	+ (With chondroidal changes)	–	–	Peripheral temporal retina with avascular area	Nasal retina: loss of the inner layers, outer layers intact; dysplastic areas Temporal retina: loss of ganglion cells, microcystoid degeneration
5	+ (Not patent)	+	– (Except for adhesion of PHV	–	Temporal retina: hypoplastic vascularization Nasal retina: fibrosis of blood vessels	Nasal retina: cystic retinoschisis
6	–	+	–	–	Hypoplastic retinal blood vessels	Retinal folds Rarefaction of inner layers
7	Not obvious	+ (With fatty degeneration	– Vitreoretinal strands	–	—	Loss of inner layers Some microcystoid degeneration
8	+	+	+	+	Peripheral temporal retina with avascular area	Loss of ganglion cells Marked gliosis

Discussion

During normal development, the hyaloid vascular system precedes retinal vascularization and undergoes involution at the seventh month. A persistent vascular system with surrounding connective tissue in the vitreous cavity is likely to be a potential factor in the induction of reactive developmental changes in other intraocular structures.

Vascular vitreoretinal anastomoses and vitreoretinal strands (Reese and Straatsma, 1958; Manschot, 1958; Wolter and Flaherty, 1959; Gärtner, 1964; Spaulding and Naumann, 1967) may be regarded as reactive tissue changes caused by disturbed involution of the primary hyaloid system.

Avascular retinal areas have previously been observed in incontinentia pigmenti or the Bloch-Sulzberger syndrome (Best and Rentsch, 1974). Our observation of peripheral avascular retinal areas in eyes of infants between the ages of one month and four years born at full-term is in contrast with that of Reese and Blodi (1949) and Reese (1955) who described a fully developed retina in PPV. The persistence of an avascular retina shows there is no need for retinal vascularization and suggests there is an adequate oxygen supply to this area of retina from the choroidal or vitreous aspects; in our cases this may be due to an increased oxygen level on the vitreous side with its abnormal vascular system (although there is also the possibility of early degenerative retinal changes and a consequent decreased oxygen demand). The same applies to a hypoplastic vascular system. The degree and morphological expression of the various factors involved (Table IV) in the abnormally developing eye may vary widely, and the lack of knowledge of the early stages of PPV would make further statements purely speculative. But with regard to vascularization of the developing intraocular tissues, especially in malformed eyes, we would expect reactions as long as involution, degeneration, and tissue growth have not reached a final stage in which the blood vessel system covers the oxygen need of the tissues sufficiently. Massive new vessel formation is a response to hypoxia which is not necessarily permanent.

According to Foos and Kopelew (1973) the retinal vascular system is complete in only 10 per cent of full-term infants. We still see oxygen-induced retrolental fibroplasia although mainly in prematurity and rarely is there an equivalent in full-term infants; thus an incomplete retinal vascularization at birth does not necessarily imply retinal

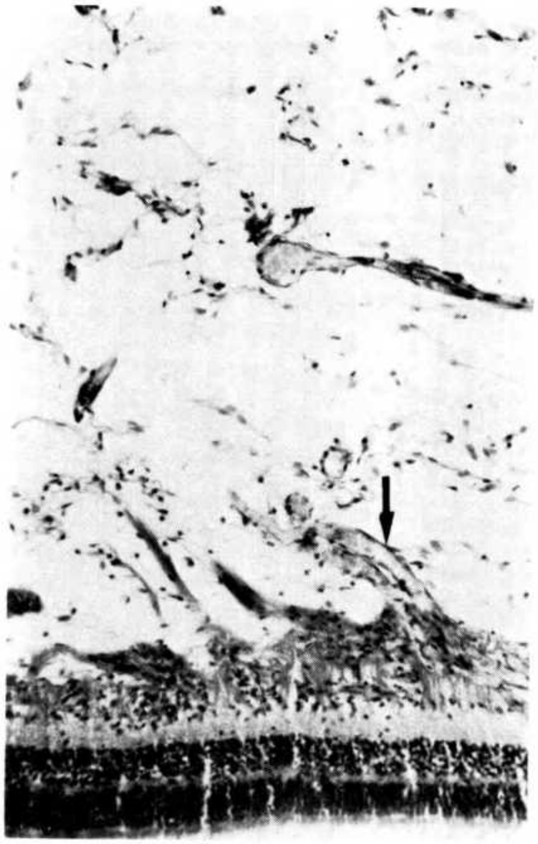

FIG. 1 *Case 1. Nasal retina showing vitreoretinal anastomosis of blood vessels (arrow) and vitreoretinal strands. Haematoxylin and eosin.* ×140

Table IV *Possible factors inducing developmental or reactive vitreoretinal changes*

Persistent primary vitreous (PPV) tissues	
	Involution
	Haemodynamics
	Hypoxia
	Degeneration
	Reactive growth
Retinal tissues	

ischaemia and with it the risk of retrolental fibroplasia. The persistence of intravitreal blood vessels, however, raises the question whether these vessels may proliferate under certain conditions and thus mimic the proliferative phase of retrolental fibroplasia. Indeed, Gyllensten and Hellström (1954, 1955), Patz (1965), and Ashton (1968) showed in animal experiments that oxygen could induce a proliferation of persistent hyaloid vessels. We noticed formations of new vessels on the surface of peripheral avascular retinal areas that had connexions with the hyaloid system and the absence of intraretinal endothelial proliferation indicates a hyaloid origin. Krümmel and Rausch (1955) and Benedikt and Ehalt (1970) have suggested that the formations of new vessels in incontinentia pigmenti are supplied from the hyaloid artery, while Best and Rentsch (1974) in their case suggested that they were supplied by the retina. So it appears possible that both vascular systems may play a role in the formation of new vessels and ischaemic retinal areas may play a pathogenetic role. This seems of importance in some hitherto unexplained cases of

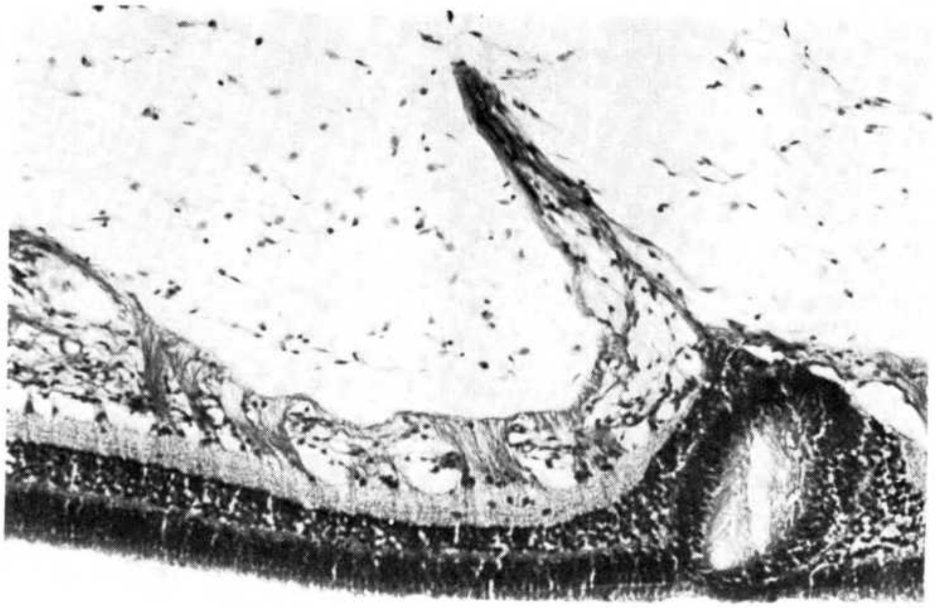

FIG. 2 *Case 1. Temporal retina with a vitreoretinal strand and formation of a retinal fold in the area of traction. Note also the ischaemic changes in the inner retina. Haematoxylin and eosin.* ×140

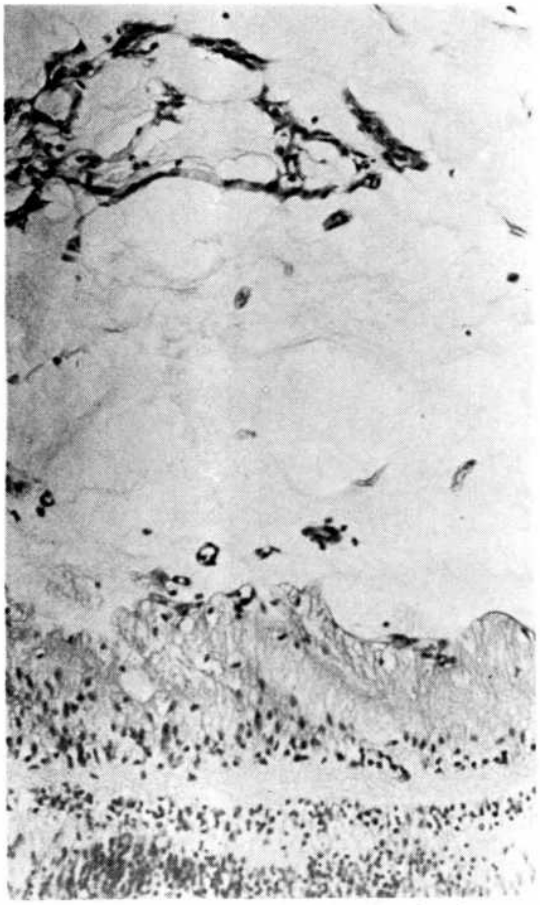

FIG. 3 *Case 2. Close spatial relationship of persistent hyaloid blood vessels to the avascular retina. Haematoxylin and eosin.* ×140

non-oxygen induced retinitis proliferans in full-term infants.

That ischaemic changes take place is further shown by the finding of microcystic retinal degenerations and the loss of ganglion cells, although changes of intraocular pressure must also be taken into account.

Summary

In cases with persistent primary vitreous in full-term infants there were vitreoretinal reactions including vitreoretinal anastomoses of blood vessels, vitreoretinal strands, traction folds of the retina, avascular retinal areas, hypoplasia of retinal blood vessels, rarefaction of retinal ganglion cells, and ischaemic structural changes of the retina. New vessel formation on the surface of avascular retinal areas was supplied from persistent hyaloid blood vessels. This finding may be of some importance in explaining those cases histologically resembling classical retrolental fibroplasia with no history of prematurity or oxygen treatment.

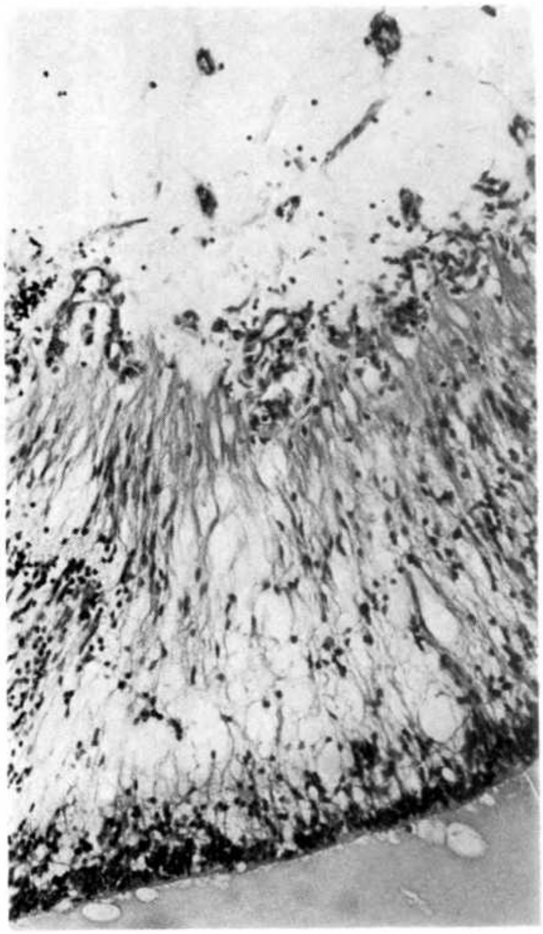

FIG. 4 *Case 2. Neovascularization on the avascular retinal surface. Retina shows marked ischaemic changes. Haematoxylin and eosin.* ×140

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Radioactive phosphorus uptake testing of choroidal lesions

A report of two false-negative tests

DENNIS M. ROBERTSON
From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation

The purpose of this report is to review the ^{32}P radioisotope uptake test as it relates to experiences with the diagnosis of suspected malignancies of the eye and to report two false-negative studies that were recorded over the posterior sclera of two eyes harbouring malignant melanomas of the choroid.

Method and materials

^{32}P testing for suspected ocular malignancy has been performed during the past three years at the Mayo Clinic in a manner similar to that described by Shields, Sarin, Federman, Mensheha-Manhart, and Carmichael (1974). Until recently our technique differed, however, in that we administered the ^{32}P orally rather than intravenously. A dose of 750 μCi of ^{32}P was given to the patient orally on an empty stomach two to six days before testing, as suggested by Ruiz and Howerton (1975). The Gass marker is used for localizing the boundaries of the suspected tumour to the scleral surface (Gass, 1966). Radioactive counts are then recorded alternately over the tumour site and at a specifically marked control site usually situated on the opposite side of the globe. We use the radioactivity detection probe and scaler (Ruiz, 1972).* Four measurements are generally recorded over each site, although more are taken if there is inconsistency in counts or if the differences between counts over control and tumour site are not obviously disparate. The percentage uptake is then determined by the formula: percentage difference $= (C_t - C_c)/C_c \times 100$, in which C_t is the average count over the suspected lesion and C_c is the average count over the control site. We consider that the test is positive if the percentage uptake over the tumour is at least 75 per cent greater than that over the control site.

Report of cases

CASE 1

A 72-year-old woman was referred with a retinal detachment in the left eye which was associated with an underlying mass located in the superior portion of the globe. Visual acuity was 20/20 in the right eye and 20/100 minus in the left. A non-rhegmatogenous retinal detachment was present, under which a raised relatively amelanotic lesion could be seen (Fig. 1*a*). The clinical findings indicated the diagnosis of a primary malignant melanoma of the choroid. A general medical examination did not reveal evidence of metastasis or a primary tumour elsewhere than in the eye. A total of 750 μCi of ^{32}P was given orally in anticipation of radioisotope testing. Three days later, the patient developed ocular pain accompanied by chemosis, congestion, and orbital swelling. Grade 2 flare and cells were present in the anterior chamber, and the vitreous contained blood originating from a haemorrhage within the tumour. Three days later (six days after receiving oral ^{32}P), a radioactive phosphorus uptake study was performed while the patient was under general anaesthesia. In spite of the vitreous haemorrhage, it was not difficult to locate the tumour and determine placement of the radioactivity detection probe (Fig. 1*b* and Table I). Although the uptake study was only 60 per cent greater over the tumour site compared with the control, the clinical findings so strongly indicated primary malignant melanoma that the eye was removed. No evidence of extraocular tumour extension was recognized to account for the recent orbital inflammation.

Histological sections demonstrated a large necrotic malignant melanoma of the choroid without evidence of extrascleral extension. Haemorrhagic choroidal detachments present in some areas caused significant thickening of the choroidal layer (Fig. 1*c*).

CASE 2

A 66-year-old woman was seen in the eye department in August 1973 with a large, raised, choroidal mass in

Table I *Radioactive counts from tumour and control sites in Case* 1 *(see Fig.* 1*)*

Counts	*Site*	*Counts/minute*	*Average*	*Percentage uptake* $= \frac{C_t - C_c}{C_c} \times 100$
Tumour (C_t)	A	72, 82, 90, 71	79	Averaging all counts: uptake = 25 per cent
	B	65, 85, 98, 105	88	
	C	69	69	
	D	55, 60, 65	59	
Control (C_c)	IN	53, 58, 51, 59	55	Highest average tumour count and lowest average control count: uptake = 60 per cent
	IT	57, 72, 79, 61	67	

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*Manufactured by EON Corporation, Brooklyn, New York.

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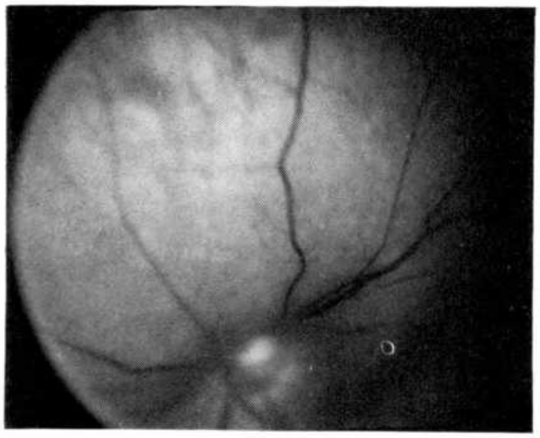

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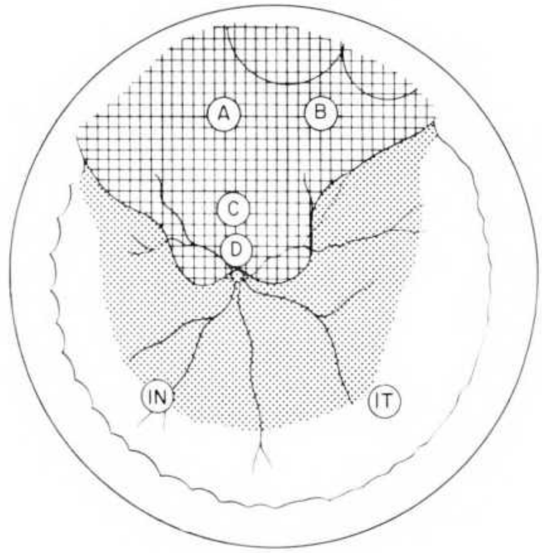

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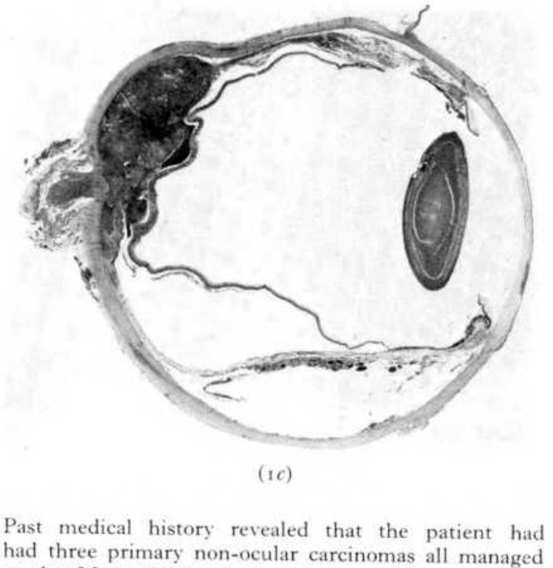


(1*c*)

FIG. 1 *(Case 1)* (a) *Fundus showing choroidal malignant melanoma superior to optic disc. Photograph taken six days before* ^{32}P *testing.* (b) *Diagram showing clinical extent of choroidal tumour (hatched) and extent of secondary retinal detachment (shaded). Labelled areas are sites of* ^{32}P *testing (see Table I).* (c) *Cross-section of eye containing necrotic malignant melanoma of choroid. Haemorrhagic choroidal detachment can be seen extending anteriorly from both sides of the tumour*

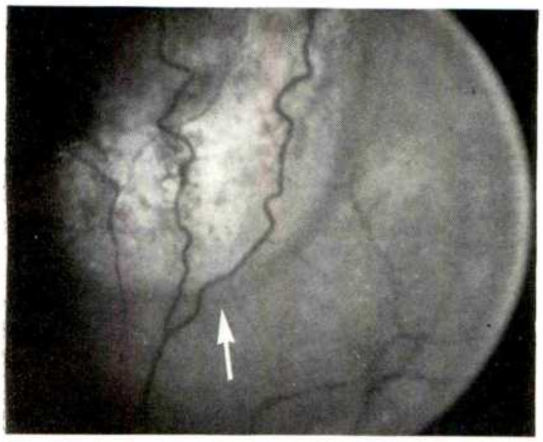
the superior portion of the left eye which was thought most likely to represent a primary malignant melanoma (Fig. 2*a*). Past records showed that a retinal detachment had been recognized in the fellow eye 13 years earlier and that there had been choroidal pigmentation in the superior nasal fundus of the left eye six years previously.

Table II *Radioactive counts from tumour and control sites in Case 2 (see Fig. 2)*

Counts	*Site*	*Counts/minute*	*Average*	*Percentage uptake* $= \frac{C_t - C_e}{C_e} \times 100$
August 1973				
Tumour	A	168, 169, 165	167	Averaging all counts:
(C_t)	B	193, 167, 185	182	uptake = 18 per cent
	C	150, 141, 155	149	
	D	155	155	
Control	IN	134, 145, 138	139	Highest average tumour count and lowest average control count: uptake = 31 per cent
(C_e)	IT	150, 139, 132	140	
April 1974				
Tumour	Random over tumour	245, 198, 335	259	Averaging all counts:
	A	387, 396, 371	385	uptake = 250 per cent
Control	IN	90, 92, 93	92	Highest average tumour count and lowest average control count: uptake = 318 per cent
	IT	86, 108, 85	93	

Past medical history revealed that the patient had had three primary non-ocular carcinomas all managed at the Mayo Clinic during the preceding 17 years. These were a grade 1 Hurthle cell adenocarcinoma of the thyroid, a grade 3 adenocarcinoma of the left breast, and at a later date a grade 3 scirrhous carcinoma of the remaining breast.

A radioactive phosphorus uptake study was done over the tumour in the left eye in August 1973, 48 hours after the patient received 750 μCi of ^{32}P orally (Fig. 2*b* and Table II). The test was interpreted as being negative. Although our clinical impression remained strong that the eye contained a malignant melanoma, the eye was not removed. In anticipation of possibly removing the eye at some future date, the fellow eye with the longstanding retinal detachment was treated with a scleral buckling procedure. Although anatomic re-attachment was achieved, the visual acuity was not



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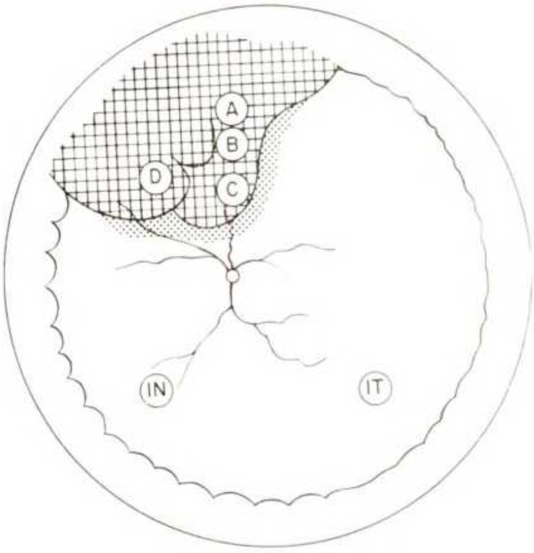
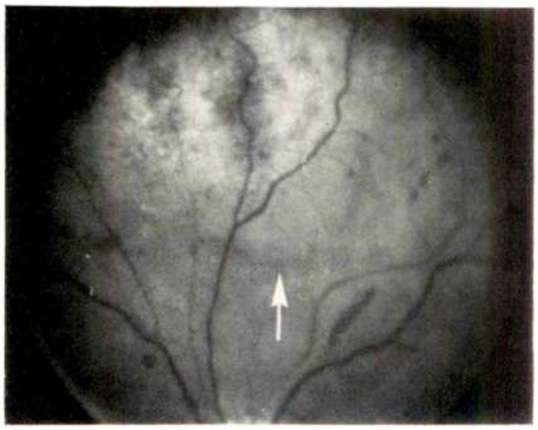


(2*b*)



(2*c*)

FIG. 2 *(Case 2)* (a) *Fundus showing most inferior extent of choroidal malignant melanoma (arrow) located superior to disc.* (b) *Diagram showing approximate clinical extent of choroidal tumour (hatched) and extent of secondary retinal detachment (shaded). Labelled areas are sites of* ^{32}P *testing (see Table II).* (c) *Fundus showing expansion of tumour (arrow). (Taken eight months after Fig.* 2a*)*

improved beyond counting fingers. During the ensuing months, tumour growth was substantiated with photographs (Fig. 2*c*). In April 1974, a radioactive phosphorus uptake study was repeated, and the result was unequivocally positive (Table II).

The poor vision in the fellow eye, the 20/20 vision in the eye containing the tumour, the age of the patient, and the history of three previously documented nonocular primary carcinomas were factors that led to a decision to consider a trial of radiation therapy. A dose of 4000 rads was given to the lesion in divided doses during a 15-day period. Although the appearance of the tumour had changed little, vision failed seven months after irradiation because of intraocular haemorrhage, and in November 1974 the eye was removed. Histological sections confirmed the clinical impression of malignant choroidal melanoma (epithelioid and spindle B-cell type).

Discussion

The ^{32}P test, which fell into disrepute in the 1950s, has again gained popularity since the development of more sophisticated and more practical instrumentation. The testing technique itself, while demanding meticulous care in the manner of probe placement, is well suited for the retinal surgeon who is accustomed to doing scleral buckling procedures which require precise localizing techniques. Proper interpretation of the test is dependent on accurate localization of the tumour to the scleral surface, just as proper management of a retinal detachment requires precise localization of retinal defects to the scleral surface. The instruments must be in proper working order, and before each test, a new voltage plateau should be determined for the radioactivity electron probe and scaler.

The two cases with false-negative results reported herein emphasize the fact that a properly performed ^{32}P test cannot be wholly relied on to make the diagnosis of malignancy. In Case 1, important factors that may have been responsible for the low radioactive counts were the haemorrhagic choroidal detachment located under the tumour and the necrosis within the tumour itself. The increased thickness of the tissue, which increased the tumour detector distance, may have been sufficient to reduce significantly the amount of radiation reaching the counting window. Also, the delay of six days from the time of ^{32}P administration to the time of testing may have been excessive, allowing significant radioactive decay.

In Case 2, we have no totally satisfactory explanation for the results being negative when the test was initially performed. Haemorrhage was not present, and the interval between administration of the radioactive phosphorus and the testing was 48 hours. Although the phosphorus may not have been absorbed from the gastrointestinal tract, administration in all our cases has been done under supervision, and patients have been given the radioactive phosphorus on an empty stomach with specific instructions to avoid ingesting antacids the day that the ^{32}P is given, since compounds such as aluminium hydroxide gel can bind phosphorus (Albright and Reifenstein, 1948). However, the negative test results may have accurately reflected a period of minimal metabolic activity within the tumour, because eight months later when the test results were strongly positive, there was unequivocal evidence of growth. In an effort to eliminate the uncertainties of ^{32}P absorption after oral administration, we currently administer the ^{32}P intravenously.

Our experience with these two cases, and that of Shields and others (1974), show that false-negative results can be recorded over lesions that later are verified as malignant melanomas. False-positive tests are also known to occur. Jarrett and Hagler (1972) reported a false-positive result of a ^{32}P test over a benign adenoma of the pigment epithelium. Metastatic lesions also generally produce a positive ^{32}P test, and whereas choroidal haemangioma can generally be differentiated from melanoma by a negative ^{32}P test result (Jarrett, Hagler, LaRose, and Shields (1975) reported no false-positive results in 29 cases) Cox (1975) recently reported three cases in which the ^{32}P test result was positive.

While the potential merits of the ^{32}P test should be considered in reducing the possibility of misdiagnosis, the relative safety of the testing procedure itself should also be considered. Seven hundred and fifty microcuries of radioactive phosphorus produce only a small dose of radiation, considering the short half-life (14 days) and the shallow tissue penetration of beta-rays (International Commission on Radiological Protection, 1970). It is about one-quarter to one-fifth the initial therapeutic dose used for the treatment of polycythaemia (Wasserman, 1976), and while the absorbed dose from 750 μCi of ^{32}P in 'standard man' is approximately 28·5 rads (International Commission on Radiological Protection, 1970), information available from the National Council on Radiation Protection and Measurements suggests that the long-term radiation risk relative to development of leukaemia and other malignancies is probably only slightly raised (National Council on Radiation Protection and Measurements, 1971). Even with repeated administration of ^{32}P for polycythaemia, haematological toxicity is usually minimal, if it occurs at all, and other complications caused by radiophosphorus are most unusual (Wasserman, 1976).

One must also consider whether the performance of the ^{32}P test in any way influences the incidence of delayed tumour metastasis. This will probably never be known because the tumour itself is so capricious, in regard to its local behaviour and to its metastasis to distant sites. Nevertheless, the ^{32}P testing procedure is accompanied by significant manipulation both in the manoeuvre associated with tumour localization and in that associated with the actual radioactive counting. Posteriorly placed probes for posteriorly located lesions may in some instances disrupt the small ciliary vessels leading to the choroid.

We have observed bleeding into and under malignant melanomas during the localizing step and are aware that others have experienced similar complications. Although there generally is no urgency in enucleating an eye with malignant melanoma, once the episcleral tissue has been disturbed, and particularly if some of the posterior ciliary vessels are injured, prompt definitive treatment would seem desirable.

While the properly performed ^{32}P test is a valuable test for determining malignancy of the posterior globe, we must guard against the tendency to underemphasize experienced clinical judgement. Whereas the ^{32}P test may in some instances prove to be more reliable than the examiners in predicting malignancy (Shields, Hagler, Federman, Jarrett, and Carmichael, 1975), the reverse may also be true, as demonstrated by Shields and others (1974) and the cases reviewed here. In such cases, clinical judgements have been superior to the ^{32}P test. The ^{32}P test must be considered in proper perspective, with the understanding that it is a laboratory test with the potential for both false-positive and false-negative results. We do not use ^{32}P testing on all eyes suspected of harbouring melanoma because in many instances the tumour is considered sufficiently characteristic that a proper diagnosis can be made without invasive techniques. We do believe, however, that it is indispensable that at least two experienced examiners should evaluate a suspicious lesion. If enough uncertainties about the diagnosis persist, the lesion may be considered then for ^{32}P testing or, alternatively, its growth can be watched with careful clinical drawings or photographs and considered for ^{32}P testing later. In rare instances, a diagnostic trial of irradiation may be considered if there is a strong possibility that the tumour is metastatic. Until a more satisfactory, non-invasive, equally reliable, and practical test becomes available for determining malignancy, however, we anticipate that the ^{32}P test will continue to be valuable as a diagnostic aid in the differential diagnosis of lesions in the eye.

Summary

Two false-negative results from ^{32}P testing for histologically verified malignant melanomas of the choroid are reported. In the first case, a haemorrhagic choroidal detachment caused an increase in the distance between the tumour and the counting probe; additionally, the tumour was necrotic. Both factors are likely to have contributed to the false-negative result. A satisfactory explanation for the false-negative result in the second case was not determined, although it may have accurately reflected a period of minimal tumour activity, inasmuch as repeat ^{32}P testing was strongly positive eight months later, when unequivocal evidence of tumour growth was present. An alternative explanation is that the orally administered ^{32}P was incompletely absorbed.

Since ^{32}P testing is frequently accompanied by significant manipulation both in the manoeuvre associated with tumour localization and in that associated with the actual radioactive counting, it would seem desirable to perform indicated enucleation immediately after completion of the ^{32}P testing.

While the properly performed ^{32}P test remains a valuable diagnostic test for helping to establish the presence or absence of malignancies of the posterior globe, it is important to guard against the tendency to underestimate careful clinical evaluation.

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Book reviews

The Effects of Blindness and Other Impairments on Early Development. Edited by Z. S. JASTRZEMBSKA. 1976. Pp. 210, 15 tables, 37 figs, refs. American Foundation for the Blind, New York ($4)

The reader will be wise to follow his own interests in approaching this compilation of papers from a conference held in 1972 at Ann Arbor, USA. The formal papers and also the comments, criticism, and discussion on each of the seven sessions are included; inevitably some of the subtleties of the issues discussed are lost in the compression of reported dialogue, but a number of the questions raised after the initial papers are pertinent and stimulating, sometimes even challenging the purpose of comparative developmental studies by questioning the point of attaining developmental milestones on schedule in the case of visually handicapped children who may in any case follow a different course from the non-handicapped in their development.

The extent to which this is so, the cause of the differences, the purpose and effectiveness of intervention are the preoccupation of the contributors, a galaxy of serious researchers many of whom have established reputations of international standing in the psychological, social, and educational aspects of blindness.

The heterogeneous nature of blindness is constantly referred to, and if there is a final impression that few conclusions are reached, then this is partly the aim and partly the result of the approach adopted. The infinite variety rather than the facile similarity of the problems is stressed, with the result that the emphasis is on an individual approach to meeting the needs of these children, with intervention based on an objective description of behavioural style.

There must have been ample supportive evidence to this approach in the films and video-tape of particular responses in individual children unfortunately unwitnessed by the reader. But there is interesting reading with the advantage of rigorous scientific study in quite specific areas of the behaviour and development of young blind children. Earlier studies, although showing awareness of some of the distinct sequels to blindness in infancy, have tended towards the global and generalized in their observations; the approach in these papers is more specific, with attempts to trace more exactly the cause of differences in response patterns between children who are blind and those who are not. There is agreement that the degree of visual impairment bears no relationship with how well the child is able to function.

Other factors with a bearing on this conclusion are considered in depth including parental attitudes towards the child and his handicap. Temperamental characteristics are identified by Dr Chase and her co-workers as major factors in the ability to overcome the handicapping effect of impairments.

The particular response patterns of the congenitally blind child are considered by Adelson and Fraiberg in papers concerned with the implication of sensory defect in infants blind from birth; Spigelman considers the effects of early blindness on the development of auditory-spatial learning, both the role of length of blindness, and the emotional reactivity of the child were shown to have a bearing on performance.

Somatosensory deprivation is the theme of Preston's substantial contribution; social deprivation as in institutional settings is an important factor for concern. The sensory basis of attachment, and the cerebellar mechanics of behaviour are also discussed.

Adelson and Fraiberg present a fascinating study of self-representation in young blind children. The observations of individual children have human interest; discussion following this paper even concentrated on some of the advantages and drawbacks of tactile vision substitute systems in the child's search for identity.

Attention is given to the problems of communication in the first three years of life for hearing-impaired children. The incidence of so many children with more than one sensory disability makes this section relevant.

Finally, some attention is given to the characteristics of particular groups of visually handicapped children. Chase and Fernandez concentrate on rubella children; signs of the difficult child are described and suggested teaching situations explored; the need for early educational intervention and for parent counselling is a recurrent theme.

These deliberations indicate how much there is to find out about the young blind child, but also add considerably to our knowledge in specific areas of inquiry.

ELIZABETH CHAPMAN

The Scientific Work of René Descartes. By J. F. SCOTT. 1976. Pp. 211, 82 figs, bibliog. Taylor and Francis, London (£8·50)

René Descartes was pre-eminently the most influential figure in the science of the 17th century; although his philosophical speculations were eventually largely discarded, he exerted a profound influence on scientific thought which in some respects still persists.

He published nothing until he was 40 years of age, but thereafter he published a series of works rarely equalled. In 1637 there appeared his *Discours de la Méthode* with its three accompanying essays, *La Dioptrique, Les Météores*, and *La Géométrie*. In the first of these, starting from the proposition 'I think, therefore I am', a statement he deemed incontrovertible, he deduced on a basis of reason a universe of three constituents—the mind, material things, and God. In *Dioptrics*, a very detailed work, he discussed his theory of light and colours, refraction and aberration, and elaborated on the optical properties of the eye and the design of lenses. In *Meteorology* he discussed the mechanism of the origin of vapours, winds and clouds and, particularly, of the rainbow. His *Geometry* was the most outstanding of the three essays and had the greatest influence on the progress of scientific thought; in it he introduced the science of co-ordinate geometry and married arithmetic, algebra, and geometry into one science as applied to straight lines, circles, curves, and solid bodies. In his final work, the *Principles of Philosophy*, he gave an elaborate and exhaustive description of his whole system of philosophy of the universe created on a mathematical model in which space is filled with matter endowed with motion which in course of time had fallen into a series of vortices in which the sun, the heavens, and the earth were carried.

Although much of this last was based on unsound mechanical principles, some of his work is extremely valuable, particularly in optics and mathematics, and was an essential prelude to the subsequent advances made by such workers as Newton. This volume provides delightful reading and is both critical and fully sympathetic; it is indispensable for anyone interested in the evolution of scientific thought, representing the first great step since the time of Aristotle. STEWART DUKE-ELDER

Symposium on Ocular Therapy, vol 8. Edited by I. H. LEOPOLD and R. P. BURNS. 1976. Pp. 92, tables, figs, refs. Wiley, New York ($12)

One's heart sinks when books with a promising title turn out to be just the collected papers from some transient congress or symposium, and not a carefully planned and balanced presentation by the distinguished names which appear on the cover. One knows in advance that the result will be a hotch-potch of papers of widely differing quality, covering isolated topics which may, nevertheless, conflict or overlap.

However, within these formidable limitations, the material here is generally excellent. The 10 'chapters' are concise and readable, with much useful information. We are told about the toxicity of drugs used for squinting children (Apt and Gaffney), with a limited message that mongols, brain-damaged children, and infants are at risk from the stronger mydriatics and miotics; that corticosteroid-resistant uveitis is helped (but rarely healed) by azathioprine and chlorambucil (Burns, Laird, and Pirofsky); about the virtues and toxicities of the local anaesthetics used in ophthalmology (Ellis); of the disadvantages of corticosteroids (Havener)—a very good account; about newer antiviral agents (Kauffman) adenine arabinoside being a good alternative for IDU-resistant or IDU-allergic cases, while trifluorothymidine, which likewise does not share allergenicity or cross-resistance with IDU, has the advantage of greater potency and water-solubility; of the factors affecting drug penetration into the eye (Lieberman); wise words about the doctor-patient relationship (Newell); about the management of bacterial corneal ulcers (Pettit); of adrenergic drugs in simple glaucoma (Sears)—concluding that the usefulness of epinephrine is proved, but that this is not yet so for the newer synthetic drugs; that, although platelet aggregation occurs in humans with diabetic retinopathy, it is not evident when this is induced by alloxan or by pancreatectomy in dogs (March, Engerman, and Shoch), an interesting finding, slightly clouded by the wry picture of those 15 beagles lining up for the chopper. P. D. TREVOR-ROPER

Xerophthalmia and Measles in Kenya. By J. J. M. SAUTER. 1976. Pp. 235. Kliniek voor Oogheelkunde, Rijks-Universiteit Groningen, Netherlands (Dfl 25)

The Dutch school of nutritionists and ophthalmologists with a special interest in malnutrition and the eye has always been conspicuous in these fields. Dr Sauter's book is a particularly successful and comprehensive account of the subject. The illustrations including several pages of colour photographs are excellent. Particular attention has been paid to vital staining of the cornea and conjunctiva, the author concluding that lissamine green has advantages over other traditional stains.

The author's particular concern was to examine the thesis that in many African countries much of the blindness was caused by xerophthalmia precipitated by the 'catalyst' measles. His conclusions were that xerophthalmia occurred nearly everywhere in Kenya in 1974, which shows that xerophthalmia is prevalent in communities which do not have rice but where maize is eaten as the staple food; xerophthalmia appeared to be the main cause of blindness in Kenyan children; measles often played, by means of local and general 'catalysing' effects, an important role in the development of blindness caused by xerophthalmia; in well-nourished children measles was of no consequence as a cause of blindness; staining by 1 per cent rose bengal or 1 per cent lissamine green appeared to be an asset in the early diagnosis of xerophthalmia in health centres and in field surveys. Staining is therefore important in the prevention of severe blindness inducing vitamin A deficiency.

Later the author performed a short additional xerophthalmia investigation in Java, Indonesia, where he examined a small number of xerophthalmia patients and children with measles keratoconjunctivitis. The result of vital staining and the corneal biopsies of these two groups of patients were in accordance with the findings in the Kenyan counterparts.

This is a fine publication, in English with Dutch summaries, and with an excellent bibliography. It deserves to be, and probably will become, a classic in this most important field of nutritional ophthalmology.

D. P. CHOYCE

Notes

Cataract Surgical and IOL Congress

Miami Beach, 5 *to* 9 *February* 1977

The fifth biennial congress will be held at the Fontainebleau Hotel, Miami Beach, Florida. There will be 70 speakers and approximately 200 papers which will be discussed by a faculty panel. Anyone wishing to present papers or films should write to the Programme Chairman, Robert C. Welsh, MD, 168 SE 1st Street, Miami, Florida 33131, USA.

Postgraduate Course in Ophthalmic Plastic Surgery

University of California, 3 *to* 4 *March* 1977

This postgraduate course at the University of California, San Francisco, will cost $150 (including lunches). Further information may be obtained from J. Earl Rathbun, MD, Programme Chairman, School of Medicine, University of California, San Francisco, USA.

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